SAMARIUM DIIODIDE-INDUCED CYCLIZATIONS

BY

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by

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This is the end of a long road. I would like to take this opportunity to thank all those who helped and assisted me during these years.

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Abstract of Dissertation Presented to the Graduate School
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August, 1991

Chairman: Eric J. Enholm
Major Department: Chemistry

The distinctive proficiency of samarium diiodide reagent in mediating ketones/aldehydes-olefin reductive cyclizations was investigated. Ketones and aldehydes tethered to electron deficient olefins were studied for the formation of carbocycles. In a single process, up to four new stereogenic centers were generated with surprising stereocontrol.

At the first stage, SmI_2 was used for the intramolecular reductive cyclization of ketones and aldehydes tethered to electron deficient olefins for the formation of simple five-membered carbocycles. The goal was to look at the olefin electronic effects in the reaction and the possible correlation of the olefin geometry in the starting substrate with regards to the product stereochemistry. With aldehyde starting materials, the (E)-geometric isomer gave a ratio only slightly favoring the anti-disposed product. In contrast, when cyclic ketones were used, a strong dependence of the product diastereoselectivity on the olefin geometry was observed. In one case, the (E)-geometric isomer produced the anti product nearly exclusively, while the (Z)-geometric isomer led to an equal anti:syn mixture of products.

This chemistry was next adapted to more complex unsaturated systems such as carbohydrates, which proved to be an excellent method for the stereoselective preparation of polyhydroxylated carbocycles. These experiments demonstrated a strong correlation in the diastereoselectivity of the products depending on whether the olefin geometry of the starting carbohydrate was E or Z. In all cases examined, the (Z)-olefin in the starting carbohydrate template favored the syn isomer and the (E)-olefin geometry favored the anti isomer.

In the last variation of this process, the proton donor in the key reaction was substituted for carbonyl electrophiles such as aldehydes and ketones. All sugar templates, upon treatment with SmI_2, underwent an initial radical olefin cyclization. Subsequently, reduction of the intermediate radical generated through this process produced a transient organosamarium enolate that was trapped *in situ* by aldehydes and ketones to produce carbocycles with two new carbon-carbon bonds.

In conclusion, these studies represent the first applications of the SmI_2 reagent to carbohydrates. Through these transformations the SmI_2 reductive procedure proved to have unleashed exciting new possibilities for stereoselective organic processes.

CHAPTER 1
INTRODUCTION

Lanthanides, also known as rare earths, were discovered and characterized from the 18th century up until the middle of the 20th century.[1] They are elements that possess a partially filled 4f electronic subshell and a xenon core. Their main oxidation state is +3, therefore Ln(IV) compounds are powerful oxidants.[2-4] The dipositive Ln(II) state is unusual for lanthanides and the only ones that can attain it easily are europium, samarium and ytterbium. In the Ln(II) state, the driving force for reactions is a single electron transfer to give Ln(III) species. Therefore, their use as reducing agents has proven very useful in organic synthesis.[5] They also exhibit rich coordination chemistry and high oxophilicity. Samarium (II) has the highest known reduction potential (Sm^{+3}/Sm^{2+} = -1.55 V) for species easily soluble in organic media, and its strong affinity for oxygen is very significant since it can be helpful in the Lewis acid activation of oxygenated organic functions.[6]

In 1977, seminal work by Namy and Kagan[7] showed that SmI_2 could be obtained by reacting samarium powder and 1,2 diiodoethane in THF and introduced it as a reagent useful for the formation of carbon-carbon bonds and the transformation of various types of functionalities.

Kagan[8] has subsequently reported a summary of these transformations which are listed in Scheme 1-1 (reactions [1] to [13]). Thus, ketones and aldehydes in the presence of protic solvents are reduced to the corresponding alcohols (reactions [1] and [2]). In the absence of proton donors

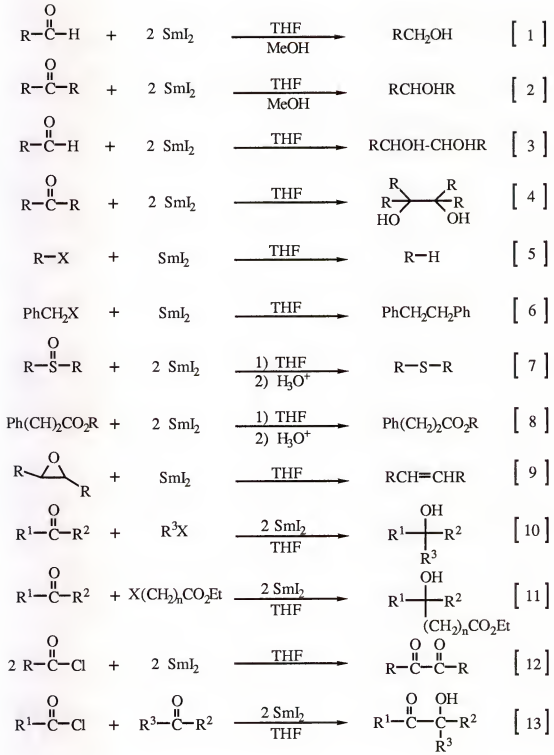
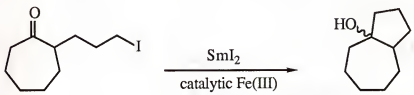

R–C(=O)–H + 2 SmI2 —THF/MeOH→ RCH2OH [1]
R–C(=O)–R + 2 SmI2 —THF/MeOH→ RCHOHR [2]
R–C(=O)–H + 2 SmI2 —THF→ RCHOH-CHOHR [3]
R–C(=O)–R + 2 SmI2 —THF→ [4]
R–X + SmI2 —THF→ R–H [5]
PhCH2X + SmI2 —THF→ PhCH2CH2Ph [6]
R–S(=O)–R + 2 SmI2 —1) THF 2) H3O+→ R–S–R [7]
Ph(CH2)2CO2R + 2 SmI2 —1) THF 2) H3O+→ Ph(CH2)2CO2R [8]
+ SmI2 —THF→ RCH=CHR [9]
R1–C(=O)–R2 + R3X —2 SmI2 / THF→ [10]
R1–C(=O)–R2 + X(CH2)nCO2Et —2 SmI2 / THF→ [11]
2 R–C(=O)–Cl + 2 SmI2 —THF→ [12]
R1–C(=O)–Cl + R3–C(=O)–R2 —2 SmI2 / THF→ [13]

Figure 1-1

Some fundamental reactions of SmI_2

pinacols are formed (reactions [3] and [4]). Conjugated esters, epoxydes and thioketones are reduced to the corresponding saturated esters, olefins, and thioethers, respectively (reactions [8], [9] and [7]), by using stoichiometric amounts of SmI_2 with or without heating. Aliphatic, vinylic, and aromatic iodides, bromides and chlorides are reduced to the corresponding hydrocarbons ([5] and [6]). Acid chlorides can be coupled with themselves to yield diketones ([12]), or with ketones to yield α-hydroxy ketones ([13]). Reductive coupling for the formation of carbon-carbon bonds using SmI_2 has also been extensively investigated by Kagan and coworkers as seen in reactions [10]-[13]. Following these initial studies, Molander and Inanaga[9] have elegantly exploited the new SmI_2 methodology. Subsequently, other chemists[9] have also elaborated on these seminal investigations.

Highly substituted five carbon rings are abundantly found in many natural products and biologically important molecules, such as enzyme regulators, the Corey lactone, and related prostaglandin intermediates.[10] Therefore, for the synthetic chemist there are good reasons for the develop-

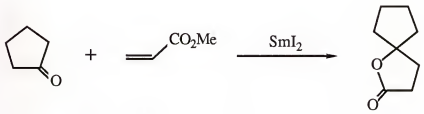


1 2

Scheme 1-2

ment of stereoselective preparation methodology. Valuable contributions in this area were made by Wilcox et al.[11] They successfully cyclized aldose

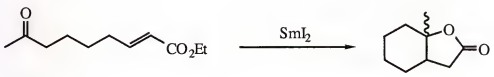
derivatives to form highly functionalized five-membered rings using tributyltin hydride. Several applications of this methodology were due to efforts by T. V. RajanBabu[12] when he showed a free radical route to the Corey lactone. Five- and six-membered rings were derived from the intramolecular reductive coupling of carbonyl groups and alkynes mediated by tributyltin hydride in the key step.[13]



3 4 5

Scheme 1-3

Over the past five years, diiodosamarium proved to be a very useful reagent for the formation of rings of various sizes. Molander and Etter[14] were the first to demonstrate the intramolecular alkylation of cyclic ketones to provide a variety of bicyclic alcohols. Thus, annulated cyclopentanols were obtained by using SmI_2 reagent, an example of which can be seen in Scheme 1-2.



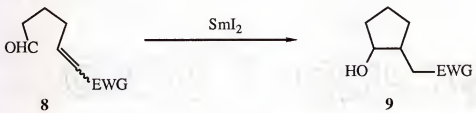
6 7

cis/trans = 36/64

Scheme 1-4

Otsubo, Inanaga and Yamaguchi[15] showed (Scheme 1-3) that γ-lactones including spiro-derivatives were formed from the intermolecular coupling of aldehydes and ketones with α,β-unsaturated esters, using samarium diodide reagent.

Fukuzawa et al.[16] were the first to show that this methodology could be expanded and utilized in an intramolecular sense for the preparation of bicyclic lactones. In substrates involving an unsaturated methyl carboxylate moiety (Scheme 1-4), the minor syn product was isolated as an annulated γ-lactone.



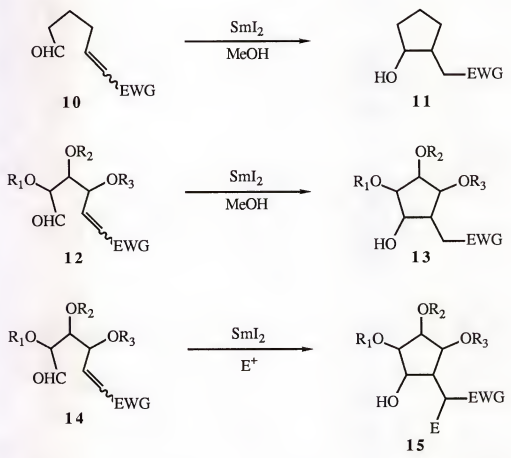
8 **9**

EWG = electron withdrawing group

Scheme 1-5

The approach in this work has been to use SmI_2 to convert acyclic substrates, with or without functional groups on the tether backbone, into carbocycles (Scheme 1-5). In more general terms, the purpose was to utilize SmI_2 for the intramolecular coupling of two sp^2 hybridized carbon centers to form two new sp^3 centers in a regiocontrolled and highly stereoselective process. This process, however, differs markedly from that of Fukuzawa in Scheme 1-4. The primary interest is in the preparation of five-membered carbocyclic rings and the examination of the effect on the

olefin geometry in the reaction. Neither one had been examined prior to this work.



EWG = electron withdrawing groups
E^+ = ketones or aldehydes
R_1, R_2, R_3 = alcohol protecting groups

Scheme 1-6

The general strategy which would permit the formation of these cyclopentanoid compounds is outlined in Scheme 1-5. When the acyclic carbonyl tethered to the α,β-unsaturated ester 8 is treated with SmI_2, a reductive cyclization between the carbonyl and the ß-carbon of the olefin

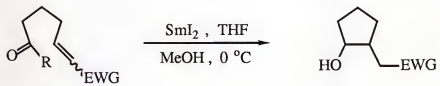
should render the desired cyclopentane system 9 in which a new C_1-C_2 bond is formed from two sp^2 centers. This key transformation (Scheme 1-5) has also been examined previously with a variety of photolytic, metal-induced, and electrochemical cyclization methods.[18]

Three levels of complexity are envisioned for this project as seen in Scheme 1-6. Initially, the simple carbonyl tethered to the unsaturated olefin would provide the most basic form of the carbocycles 11. In an intermediate level of complexity, highly functionalized, optically active carbocycles 13 could be obtained from carbohydrate templates 12 by an analogous approach. It should be noted that existent 5-hexenyl free radical methods for the cyclization of carbohydrates, such as those developed by Wilcox and Rajanbabu, do not allow for the incorporation of this additional sp^3 alcohol center which provides an extra functionality for subsequent synthetic manipulations. Finally, the elaborated carbocycle 15 with substituents at every carbon of the ring as well as an exterior functionality outside of the ring was targeted by using carbonyls as electrophiles. A great measure of stereocontrol in the formation of the new carbon-carbon bond was obtained in all of these transformations.

CHAPTER 2

SIMPLE CASES

The key process, shown in Scheme 2-1, outlines the basic reaction that was first examined.[17] As mentioned earlier, many investigators[18] have probed this transformation using a variety of other reagents, but most of these approaches suffer from a number of drawbacks such as strong reducing reaction conditions, incompatibility with several functional groups, and the formation of a variety of side products. This reaction then will be reexamined here as a method to prepare disubstituted five-membered rings. The goal is to look at the olefin electronic effects in the reaction and the possible correlation of the olefin geometry in the starting substrate with regards to the product stereochemistry, which have been little examined prior to this work.



16 **17**

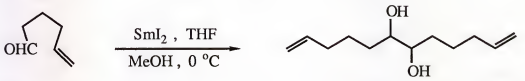
48-87%

R = Alkyl, H
EWG = CO_2Me, CN, Ph

Scheme 2-1

The conditions of the key reaction employed 2 equivalents of SmI_2 at 0 °C under dilute conditions (~ 0.050 to 0.025 M solution in the starting

substrate) with methanol as a proton donor. The preparation of the SmI_2 reagent was easily done by stirring finely ground Sm metal (6.00 g) in THF (200 mL; 0.1 M) along with 1,2-diiodoethane under Argon atmosphere and allowed to reflux for 6 h. The dark blue reagent could then be stored in the refrigerator over a period of 3-4 months with little or no loss of activity.



18 **19**

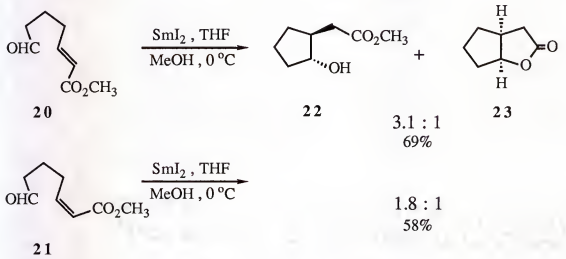
Scheme 2-2

In these tranformations, aldehydes or ketones tethered to several electron-withdrawing groups (EWG) such as methyl carboxylate, nitrile, and phenyl were investigated (Scheme 2-1). The yields for these reactions were satisfactory (48-87%) for nearly all cases attempted. The electron withdrawing group was apparently necessary for the cyclization to occur because when 5-hexanal was reacted under the above conditions, only the pinacol coupled product 19[19] could be isolated in 74% yield rather than the reductively cyclized product (Scheme 2-2). Curran[9(d)] has recently applied this reaction to the synthesis of linearly-fused triquinanes in a key step in which the aldehyde-alkene substrate lacked an electronically deficient alkene; thus, it is apparent that some substrates do not require the engagement of activated olefins.

Aldehyde-Alkene Couplings

In order to study the reaction in more depth than previous investiga-

tors, it was decided that the effects on the olefin geometry be examined. The first set of reactions involved the use of an aldehyde carbonyl connected to an unsaturated methyl carboxylate as an electron withdrawing group, as illustrated in Scheme 2-3.

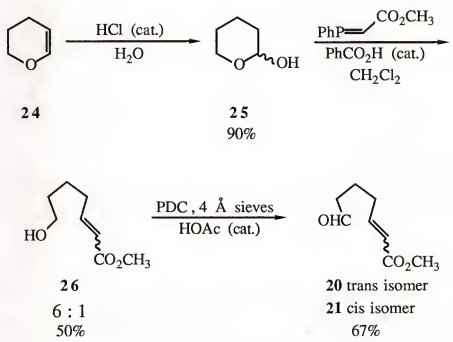


Scheme 2-3

Thus, trans olefin 20 and cis olefin 21 were subjected to the SmI_2 conditions and produced a mixture of the anti 22 and the syn 23 cyclic alcohols at ratios 3.1:1 (anti:syn) and 1.8:1 (anti:syn) respectively. The yields were 69% for the two products, when the trans olefin 20 was used, and 58% when the cis olefin 21 was reacted. The minor syn product 23 was expected to be isolated as an annulated γ-lactone as was also observed by Fukuzawa and coworkers.[16]

The substrates 20 and 21 used in these reactions were prepared as seen in Scheme 2-4 from commercially available 1,2-dihydropyran. Dihydropyran 24 was treated with a catalytic amount of concentrated HCl in the presence of water as solvent. This simple alkene hydration reaction was

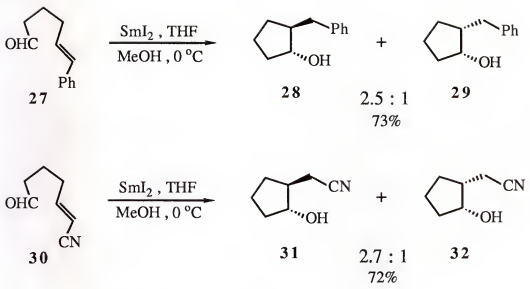
complete in a few minutes and the lactol 25 was obtain in a 90% yield. The crude mixture was then subjected to the standard conditions of a Wittig reaction with methyl triphenylphosphoranyl. Product 26 was obtained in a 50% yield as as mixture of two isomers (6:1; trans:cis) which were separated by flash chromatography. Pyridinium dichromate oxidation on each of the two isomers rendered cis and trans isomers 20 and 21 respectively.



Scheme 2-4

Following the same route of preparation, other aldehydes employing the trans geometry on the double bond and different electron withdrawing groups were prepared. Substrates 27 and 30 were subjected to the SmI_2 conditions as seen in Scheme 2-5. Aldehyde 27 gave a mixture of two isomers 28 and 29 in a total of 73% yield and a ratio of 2.5:1. Aldehyde 30 gave about the same ratio (2.7:1) of the two anti and syn products.

In all cases examined the major diastereomeric product that was ob-



Scheme 2-5

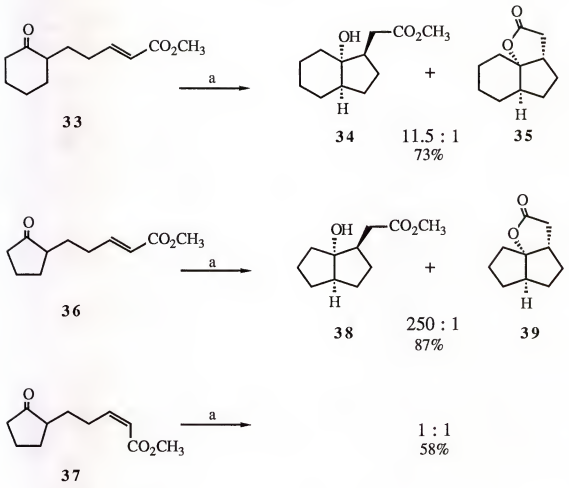
served possesses the anti relationship between the hydroxyl and the substituted methylene appendage about the newly formed σ-bond. Confirmation of the streochemistry of the products was achieved by spectral comparison with known compounds.[20] It is also important to note that the conditions in these experiments were varied with the hope of improving the diastereomeric ratios. Lowering the temperature to -30 °C and -78 °C did not seem to improve the diastereoselectivity. Proton donors other than methanol were used such as t-butanol, ethanol and isopropanol, but no differences in the ratio of products or the yields were observed. The presence of a proton source was important, however, because in experiments were it was omitted, complex unidentified products were formed. It was also critical that the proton source was present in the reaction mixture during the entire time process. Thus, the starting material was drawn into a syringe along with methanol and THF and added to the cold, stirred SmI_2-THF solution dropwise over several minutes. Experiments where the methanol was added subsequent to the addition of the starting material into the reagent

failed to give any products. The yields in these reactions were modest because of the high propensity of aldehydes to undergo coupling and yield pinacolic products. In all cases the pinacol product was also isolated in yields ranging between 10-15%. In exploring the scope of this reaction it was important to determine the effects of chain length in the type of products formed. Thus, the synthesis of six- and seven-membered carbocycles was attempted by increasing the length of the carbon chain, between the aldehyde and the alkene moiety, of compound 20 by one and two carbon units. In both cases, even though cyclic products were formed, the investigation was soon dropped because other unidentified products had also formed and the yields were relatively poor.

Ketone-Alkene Couplings

Unfortunately, in the studies of aldehydes, the (E)-geometric isomer gave only a slightly better ratio favoring the trans disposed product. In marked contrast, when ketones were studied (Scheme 2-6) a strong dependence of the product diastereoselectivity on the olefin geometry was observed. Cyclopentanone (E)-geometric isomer 36 produced 38, the anti product, nearly exclusively (>250:1), while the (Z)-geometric isomer 37 led to an equal anti:syn mixture of 38 and 39 respectively. In the case where the (E)-cyclohexanone 33 was used the anti isomer was again favored to the syn product 35 by a ratio of 11.5:1.

Although pinacolic coupling products were observed in all of the examples involving aldehydes, no such coupling was observed with the ketones. This is likely due to the steric hindrance that the ring provided, thus making it difficult for the two ketyls to couple.



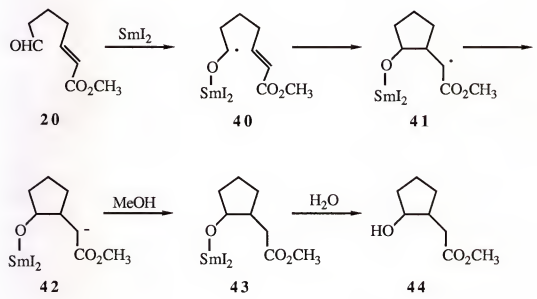
KEY : (a) SmI_2 , THF, MeOH, 0 °C

Scheme 2-6

Mechanistic Considerations

Kagan and coworkers[5] in their pioneer work have established that a radical mechanism probably mediates these reactions. Fukuzawa[16] has proposed that the initial reaction involves the transfer of one electron from Sm^{+2} to the carbonyl and the generation of a ketyl radical 40. The ketyl formation is followed (Scheme 2-7) by radical addition to the electron-

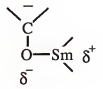
deficient double bond yielding a stabilized alkyl radical 41 which then accepts one more electron from SmI_2 to produce anion species 42. Subsequent rapid protonation by the methanol yields the desired products 44. Another mechanistic possibility is that the radical produced after the cyclization abstracts a hydrogen atom from the solvent more rapidly than it is reduced by a second equivalent of SmI_2. However, failure to get any of the desired products in the experiments when the proton source was omitted could indicate that the hydrogen abstraction from the solvent does not happen in a substantial degree, if it happens at all.



Scheme 2-7

In an earlier report on the mechanism on SmI_2 reactions, Kagan, Namy and Girard[6(e)] suggested the possibility of electron transfer to the ketone which would lead to an alcoholate anion 45 seen in Figure 2-1, which could then attack the electron-poor olefin in a Michael fashion. This, however, is not in agreement with the formation of pinacols when

aldehydes were used as starting material. It is also unlikely that this strongly basic species will exist in the presence of a proton donor.

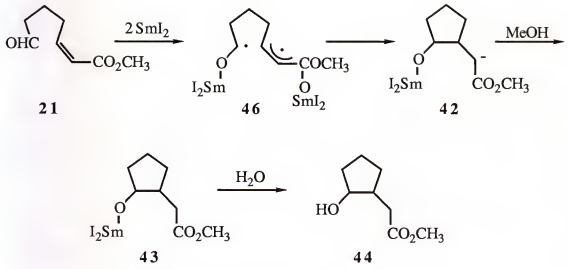


45

Figure 2-1
Alcoholate anion

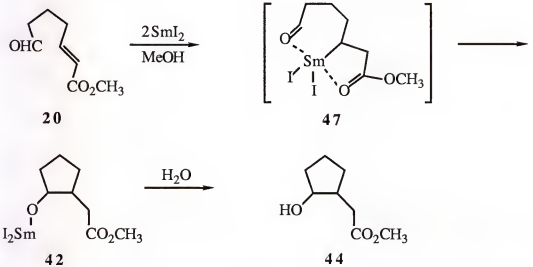
From the outset of this work, it was not clear whether the α,β-unsaturated ester could be an electron-acceptor from SmI_2 along with the carbonyl. Indeed, both functional groups possess similar electrochemical reduction potentials.[18] Recent polarography studies by Little and coworkers have indicated that the unsaturated ester is the electrophore in systems such as those shown in the previous schemes.[18(f-g)] Therefore, there is a possibility that SmI_2 transfers an electron to the conjugated ester as well as to the carbonyl, thus forming an allylic radical 46 with subsequent coupling of this to the ketyl radical, followed by the incorporation of a hydrogen by the alcohol into the α-carbon of the ester group 43, as seen in Scheme 2-8. Thus, at present it cannot be established that double bond isomerization does not occur and whether the products are in fact the kinetic products of the reaction.

In this mode of thought then, two things needed to be considered. At first, the possibility that cyclizations may be and probably are reversible at the radical anion stage and secondly, if an initial reduction of the double bond could also be established. Although the former can explain some later



Scheme 2-8

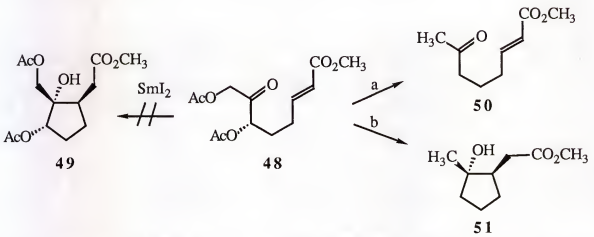
results (Chapter 4), an ionic mechanism involving a samarium ester homoenolate (Scheme 2-9), was ruled out early in these studies. Such a mechanistic possibility would involve two successive one electron transfers



Scheme 2-9

from 2 equivalents of SmI_2 to the conjugated ester to afford a samarium ester homoenolate 47. The samarium homoenolate intermediate then would

add to the carbonyl in a nucleophilic addition fashion to form substrate 42 which upon aqeuous work up would render product 44.

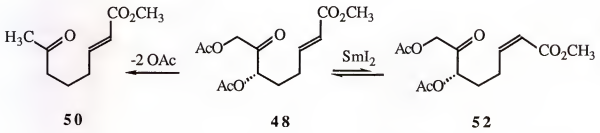


KEY : (a) SmI_2 (4 eq.), THF, MeOH ; (b) SmI_2 (5 eq.), THF, MeOH.

Scheme 2-10

As a mechanistic probe, in order to elucidate this possibility, the diacetate 48 was prepared as seen in Scheme 2-10. In this experiment, when 48 was treated with an excess (4 eq.) of SmI_2, compound 49, the expected product from the one-electron reduction of the unsaturated ester, was not observed, rather, compound 50 was isolated in which both acetoxy moieties have been reductively cleaved. Molander and Hahn[22] have recently shown that α-acetoxy ketones rapidly eliminate acetoxy functionalities when they are treated with 2 equivalents of SmI_2 in THF-methanol solution at -78 °C. When 48 was treated with 5 equivalents of SmI_2, the racemic alcohol 51 was isolated in which reductive cyclization had finally occured. These results do not support the mechanism proposed in Scheme 2-9 and indicate that the acetoxy functional groups are cleaved faster than the reductive cyclization occurs. When benzyl ethers were used instead of acetoxy groups,

a product almost identical to compound 49 (with benzyl ethers and the stereochemistry shown) was obtained (Chapter 3) with 2 eq. of SmI_2.



50 **48** **52**

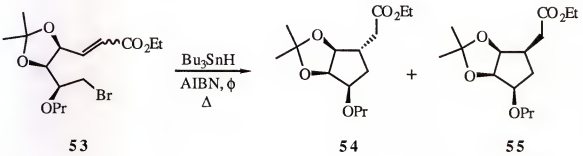
Scheme 2-12

One possibility that has not been ruled out, along with the proposed mechanism in Scheme 2-8, is that the unsaturated ester initially accepts a single electron from SmI_2 and a subsequent electron transfer through space occurs,[23] followed by cyclization on the olefin. If this initial step of the mechanism is reversible and the allyl radical is formed then an olefin isomerization would be expected if, instead of working with the E geometry on the double bond as in compound 48, a compound was used such as ketone 52 in Scheme 2-11. Thus, if 52 is made available and trans compound 50 is obtained from treatment with 4 eq. of SmI_2 and stopping the reaction prior to completion, then the above suggestion and the mechanism proposed in Scheme 2-8 could not be ruled out and there is a good possibility that the unsaturated ester is accepting an electron and possibly acting as the electophore in these systems.

CHAPTER 3

CARBOCYCLES FROM CARBOHYDRATES

Even though SmI_2 chemistry has never before been applied to carbohydrate chemistry, many creative free radical approaches to the preparation of carbocycles from carbohydrates have been recorded.[24] Wilcox and Thomasco[11(a)] were the first to use radical chemistry for the successful cyclization of aldose derivatives. Aldose derivative 53, seen in Scheme 3-1,



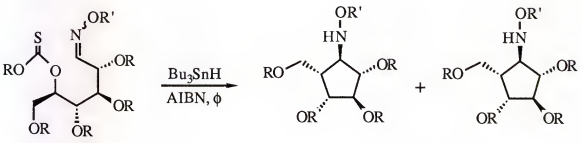
53 **54** **55**

Pr = H, $COCH_3$, COC_6H_5, $COC(CH_3)_3$

Scheme 3-1

was heated with Bu_3SnH/AIBN in benzene and both geometric isomers (Z and E) afforded the same two isomeric products 54 and 55 in excellent yields, albeit in different ratios. Their ratios did not depend on the olefin geometry but on the nature of the protecting group at the C-6 hydroxyl. These experiments established that the usage of radical-olefin cyclizations may be extended into structurally complex carbohydrates without complications. Very soon, more applications of radical chemistry to poly-

oxygenated substrates proved to be a very powerful synthetic protocol and has since found use in the preparation of biologically active polyhydroxylated carbocyclic natural products. The conditions required for such a carbon-carbon formations are mild, and asymmetric carbon nuclei can be retained next to sites of bond formation. Other problems, such as interference of the carbohydrate protecting groups with two electron or anionic methods, are avoided by using one electron or radical methodology.



56 **57** **58**

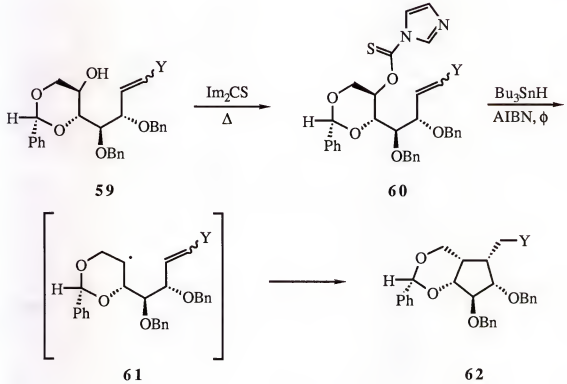
OR = protecting group
OR' = methyl or benzyl group

Scheme 3-2

In 1988, Bartlett et al.[25] (Scheme 3-2) used protected glucose hemiacetals which he converted into phenyl thionocarbonates bearing a methyl or benzyl oxime 56. He subsequently used tributyltin hydride to induce cyclization of these materials and he obtained carbocycles 57 and 58.

RajanBabu[26] demonstrated (Scheme 3-3) that aldopyrananoses readily undergo the Wittig reaction to give hex-5en-1-ols 59 which he subsequently converted into highly functionalized hex-5-enyl radicals by a variation of the Barton reaction. The radical 61 then induced a cyclization that

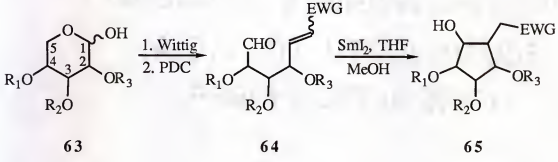
lead to predominant or almost exclusive syn product 62 in all sugars examined regadless of the starting olefin geometry.



Scheme 3-3

This work achieves a quite different solution to the transformation of carbohydrates to carbocycles by using SmI_2 reducing reagent in a mild and regiocontrolled ring-forming process.[27] This study also demonstrates a strong correlation in the diastereoselectivity in the products depending on whether the olefin geometry of the starting carbohydrate template is E or Z. Finally, this represents the first application of SmI_2 to carbohydrate templates.

The general strategy which permits the conversion of pyranose sugars into highly oxygenated cyclopentanoid compounds can be seen in Scheme 3-4. Thus, protected carbohydrate lactol 63 can undergo a Wittig reaction with a stabilized ylid and subsequent pyridinium dichromate oxidation to produce substrate 64. When 64 is treated with SmI_2 reagent a reductive cyclization between the carbonyl and the β-carbon of the olefin then renders the desired polyhydroxylated cyclopentane compound 65, in which a new C_1-C_5 bond (carbohydrate numbering) is formed between two sp^2 centers.

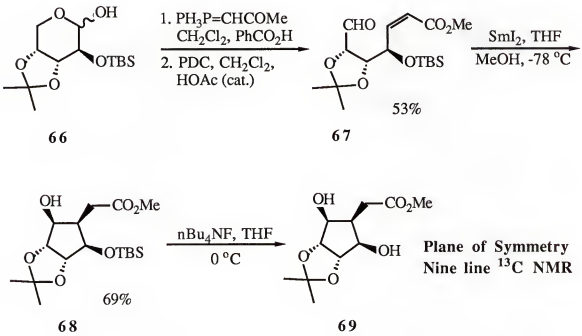


63 64 65

Scheme 3-4

In a general experiment, the carbohydrate template is dissolved in THF-MeOH (3:1; 1.00 mL) and drawn into a syringe. Samarium diodide (0.10 M in THF, 3.0 eq) is cooled to -78 °C and the solution of the carbohydrate is added dropwise over 15 minutes. After several minutes, the reaction is generally complete by TLC analysis and quenched with aqueous saturated $NaHCO_3$ and extracted with ethyl acetate. Condensation and flash chromatography produces then the densely oxygenated cyclopentanes. The afformentioned sequence was reduced to practice when 66, readily available in four steps from D-(-)-arabinose was converted to the acyclic

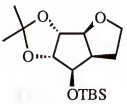
alkene aldehyde 67 by Wittig condensation and then oxidation in 74% and 73% yields respectively, shown in Scheme 3-5. The Z geometric isomer



66 **67** **68** **69**

Scheme 3-5

(major product) was isolated in a ratio of 10:1 Z:E, from the 4:1 Z:E olefin mixture by double flash chromatography. This reversal in stereochemistry from the normally favored trans product expected from a stabilized ylid has

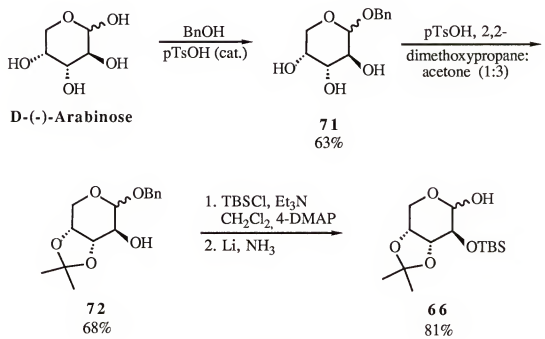


70

Figure 3-1

Arabinose cyclic ether 70

been observed with other carbohydrate lactols. The C-5 hydroxyl functionality appears to play a role in the formation or decomposition of the oxophosphotane intermediate in the Wittig reaction. This effect was recently observed in furanose sugars and it was strongly dependant on the type of carbohydrate examined.[24] Subsequent treatment with SmI_2 in the presence of methanol as a proton donor produced an almost exclusive stereochemical result (99:1 by capillary GC analysis), 68 in a 69% isolated yield. It is noteworthy that a single stereochemical result was obtained from four possible products. A small amount (<10%) of the dimerized carbohydrate product which was incompletely identified was also present in the reaction.

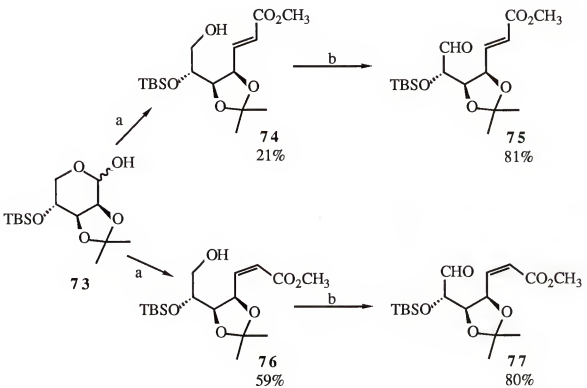


Scheme 3-6

The syn stereochemistry in the major product was uniquivocally established by both 2-D NOESY experiments and by chemical structure transformations. Thus, a plane of symmetry was revealed by removing the

t-butyldimethylsilyl group, giving syn diol 69 which has the stereochemistry shown in Scheme 3-5 from a simple ^{1}H NMR and a 9 line ^{13}NMR.

Although compound 68 resisted several attempts to undergo lactonization, formation of the bicyclic ether 70 (Figure 3-1) confirmed the syn stereochemistry of 68. The cyclization was achieved by a three step treatment with lithium ammonium hydride in THF as a first step, followed by treatment with triphenyl phosphine and carbon tetrabromide in CH_2Cl_2 and finally by using NaH in THF.[28]

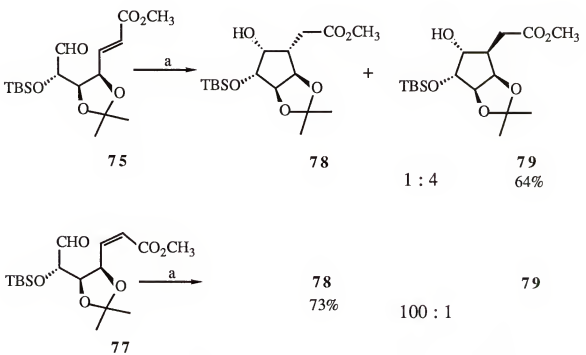


KEY : (a) $PH_3P{=}CHCO_2Me$, CH_2Cl_2, $PhCO_2H$; (b) PDC, CH_2Cl_2, HOAc (cat.)

Scheme 3-7

Lactol 66, the starting substrate used in this study, was prepared by first reacting the starting sugar D-(-)-arabinose with benzyl alcohol and a

catalytic amount of p-TsOH which rendered compound 71. Treatment of triol 71 with a 3:1 mixture of acetone:2,2-diethoxypropane in the presence of a catalytic amount of p-TsOH rendered compound 72 in a 68% yield. Protection of the C-2 hydroxy group was achieved by reacting 72 with TBSCl in the presence of Et_3N and a catalytic amount of 4-DMAP using CH_2Cl_2 as a solvent. Finally, lactol 66 was obtained by using standard deprotection methods for removing a benzyl group and reestablishing the hydroxy group. All other carbohydrate lactols were prepared using this exact same procedure described in Scheme 3-6.

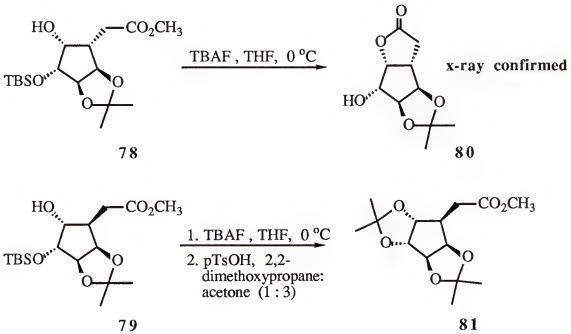


KEY : (a) SmI_2, THF, MeOH, -78 °C.

Scheme 3-8

In another example of the reductive cyclization process, shown in Scheme 3-8, the relationship of the olefin geometry in the starting substrate

vs. the product diastereoselectivity of the new σ-bond was examined. Therefore, the α,β-unsaturated esters 76-cis and 74-trans were obtained by a standard Wittig reaction as a ca. 3:1 geometric mixture from the protected D-lyxose lactol derivative 73 in 59% and 21%, respectively, as illustrated in Scheme 3-7. Note that the trans:cis ratio is reversed again since 76-cis is the predominant product. After separation, both 74 and 76 were oxidized to give aldehydes 75 and 77 in 81% and 80% yields respectively. When 75-trans was treated with SmI_2 (Scheme 3-8), two polyoxygenated cyclo-pentane products were observed in a 4:1 ratio, 79-anti, and 78-syn, respectively, from which the major product was obtained in 64% yield. In marked contrast, when 77-cis was treated under identical conditions, 78-syn was obtained as an almost exclusive product (100:1 by capillary GC analysis) which was chromatographically isolated in 73% yield. No other products (>2%) were observed in either reaction.



Scheme 3-9

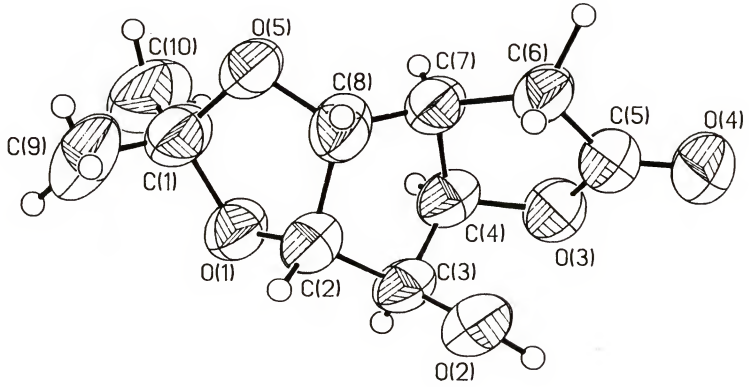
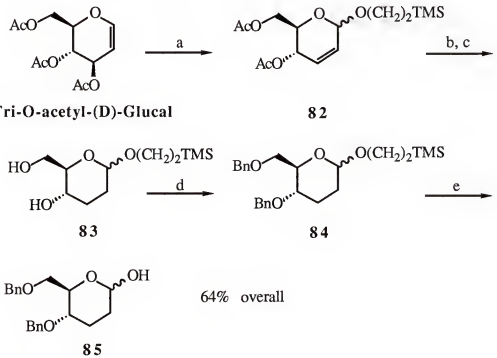


Figure 3-2

Crystal x-ray structure for carbocycle 80

The stereochemistry of 78-syn was confirmed (Scheme 3-9) by removal of the tert-butyldimethylsilyl protecting group which caused simultaneous γ-lactonization to produce tricyclic alcohol 80. A subsequent x-ray structure determination confirmed the stereochemistry as shown. The stereochemistry of 79-anti was confirmed by removal of the tertbutyldimethylsilyl protecting group which did not cause concomitant lactonization in this case. This suggested that the two new appendages were anti disposed to each other. Fortunately, standard acetonide formation prepared tricyclic methyl ester 81 and demonstrated that the two alcohols were cis disposed on the cyclopentane ring. Because 79-anti is indeed spectroscopically dif-

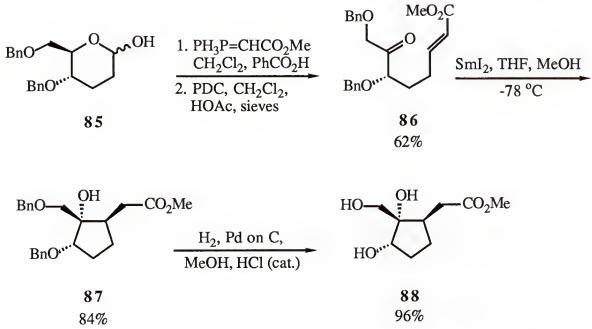


KEY : (a) $(CH_3)_3Si(CH_2)_2OH$, BF_3-OEt_2 (cat.), ϕ, 23 °C; (b) H_2, EtOAc, Pd on C (10%); (c) K_2CO_3, CH_3OH; (d) NaH, BnBr, THF, reflux; (e) CF_3CO_2H, CH_2Cl_2, 0 °C.

Scheme 3-10

ferent from the 78-syn, this confirms that the methyl ester appendage must be β-disposed in tricycle 81.

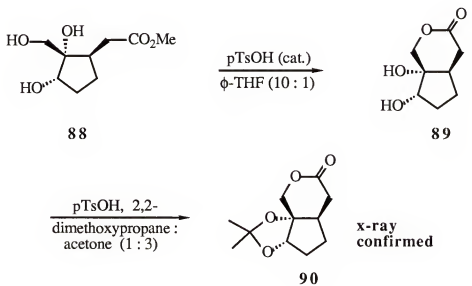
Another example was obtained by substituting the aldehyde carbonyl with a ketone such as the tri-O-acetyl-(D)-glucal could provide. Lactol 85 was prepared from the starting carbohydrate as illustrated in Scheme 3-10. The starting sugar substrate was subjected to a reaction with trimethylsilyl ethanol in the presence of BF_3-OEt_2 and benzene which inserted the silyl protecting group at the anomeric center and at the same time displaced the acetate group by moving the double bond to obtain compound 82. Hydrogenation of compound 82 and then treatment with potassium carbonate removed the protecting groups and afforded diol 83. Benzyl protecting



Scheme 3-11

groups were introduced by treating 83 with sodium hydride and benzyl bromide. Finally, the hydroxyl group at the anomeric center was reestab-

lished by treating 84 with trifluoroacetic acid. These reactions proceeded rapidly and they were clean enough so that the sugar substrate could be subjected to the next reaction without purification. At the last step, flash chromatography rendered lactol 85 in a total of 64% yield for all five steps.



Scheme 3-12

Lactol 85 then went through the standard Wittig and PDC oxidation transformations to give ketone 86 in a two step 62% yield. This trans olefin tethered to the ketone was subjected to the standard SmI_2 conditions and a mixture of two products was obtained (ca. 3:1), carbocycle 87 being the major one in a total yield of 79% after chromatography. In order to prove the stereochemistry of the major compound, 87 was subjected to hydrogenolysis by treatment with H_2 in the presence of methanol, Pd on C and a catalytic amount of hydrochloric acid. Thus, triol 88 was isolated in a 96% yield as a thick oil. It was necessary then to resort to chemical transformations in order to establish the stereochemistry of the major product of the reaction. Compound 88 was treated with p-TsOH in the presence

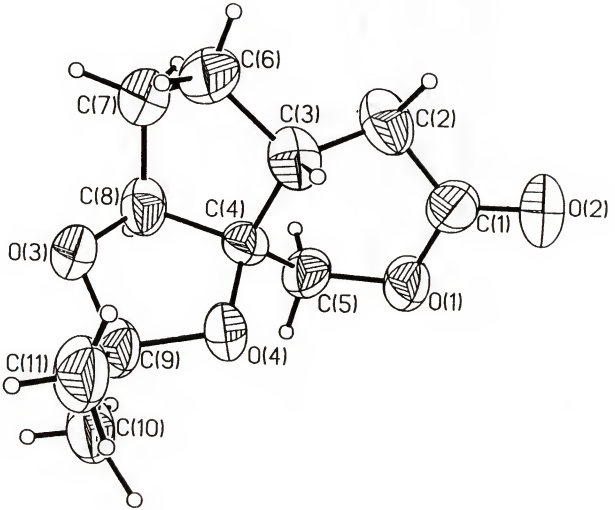
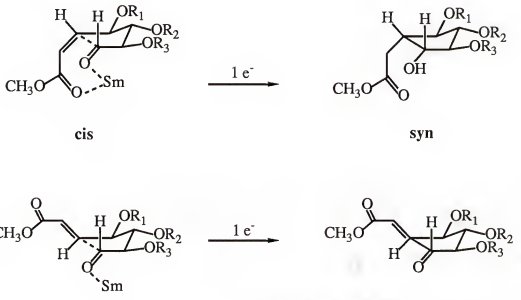


Figure 3-3

Crystal x-ray structure for carbocycle 90

of benzene:THF with the hope of forming a five-membered lactone between the new appendages of the sp^3 bond, if indeed these two were syn disposed to each other. However, a six-membered lactone 89 was obtained indicating that perhaps the aforementioned appendages were anti disposed to each other. This result lead to the hypothesis that the two hydroxy groups had the syn stereochemistry and therefore, they should easily be tied with an acetonide group. Thus, compound 89 was treated with p-TsOH and a 1:3 mixture of 2,2-dimethoxypropane:acetone and luckily lactone 90 was obtained in crystaline form. An x-ray of the crystals confirmed the fact that the hydroxyl group was pointing to the α-face and the carboxylate moiety towards the β-face.



Scheme 3-13

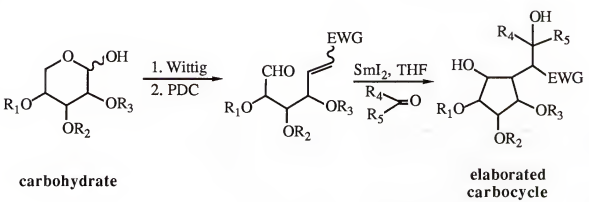
The most interesting observation in these examples is the correlation of the olefin geometry in the starting substrate with the product stereochemistry. Although these studies involve only a few examples, it would

appear that a cis-olefin in the starting substrate favors a syn product and a trans-olefin favors an anti product. At this stage, it is reasonable to assume that a chelate involving oxygen and Sm(III) is best accomodated by the cis olefin thus yielding a syn product. The trans starting substrate gives the anti product (Scheme 3-13). A seven-membered (cis) chelate ring cannot easily accomodate a trans olefin if we assume that the two sp^2 carbons are brought within bonding distance. This correlation is perhaps improved by the presence of the acetonide ring on the carbon backbone, which adds rigidity to the transition state and further, it limits the degrees of freedom.

CHAPTER 4

SEQUENTIAL RADICAL CYCLIZATION--CARBONYL ADDITION

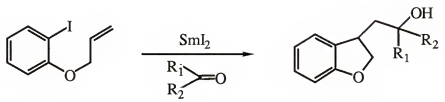
As demonstrated in Chapter 3, radical cyclizations mediated by SmI_2 provide an attractive path by which carbocycles can be generated from carbohydrates. In all cases previously examined, the SmI_2-mediated cyclizations were terminated by a proton abstraction from the proton donor. Stepping up the ladder of complexity, a more sophisticated process has been envisioned in which radical cyclization can be followed by a second carbon-carbon bond-forming process. The objective, demonstrated in Scheme 4-1, was to examine the sequencing of a one-electron cyclization to produce



Scheme 4-1

a carbocycle and to subsequently couple it via a two-electron condensation with a carbonyl in order to produce a more complex carbocycle. Thus, in a single process, two carbon-carbon bonds are formed and a highly functionalized carbocycle is generated. In these reactions, up to four new

stereogenic centers are created from a single existing transformation with high stereoselectivity.

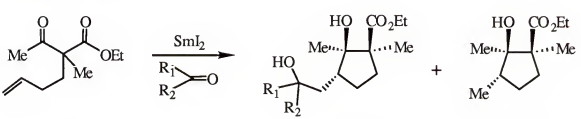


91 **92**

R_1 = H, R_2 ; R_2 = alkyl, aryl group

Scheme 4-2

Very recently, when the methodology herein had acheived excellent results, three related publications established the success of the above process on simple nonoptically active substrates. Dennis Curran[29] almost concurrently with Molander showed that SmI_2 mediates aryl radical cyclization of 1-allyloxy-2-iodobenzene in the presence of hexamethyl phosphoric triamide and produces a solution-stable organosamarium intermediate that can be trapped with a variety of electrophiles including aldehydes and ketones to yield heterocyclic derivatives. A general example of this process can be seen in Scheme 4-2 above. Little stereocontrol was observed in these early attempts.



93 **94** **95**

R_1 = H, R_2 ; R_2 = alkyl, aryl group

Scheme 4-3

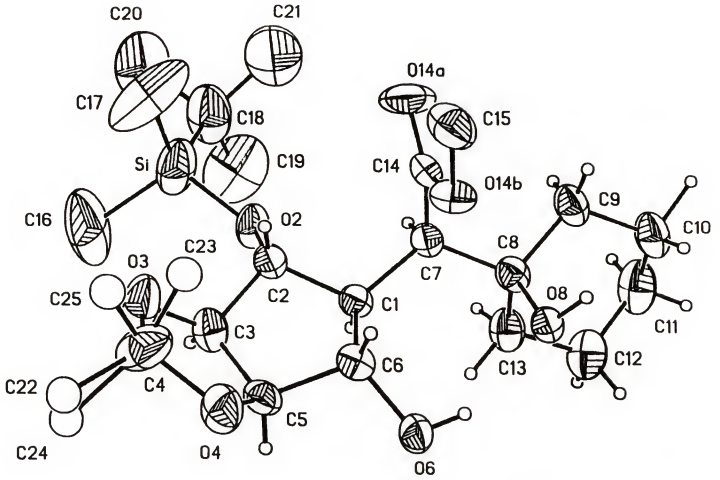
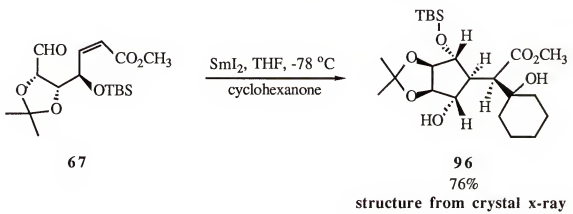


Figure 4-1

Crystal x-ray structure for carbocycle 96

Later, Molander and Kenny[30] applied the same concept to unsaturated β-keto ester 93 in a condensation with a variety of aldehydes and ketones to yield products 94 and 95 as seen in Scheme 4-3.

The course on the sequential radical cyclization/intermolecular carbonyl addition reaction in these studies started with the study of the reaction of arabinose derivative 67 and a symmetrical ketone such as cyclohexanone (Scheme 4-4). Starting material was mixed with an excess (2 eq.) of the ketone and subjected simultaneously at the SmI_2-THF solution. The only detectable product was (96), isolated by flash chromatography in 76% yield. The structure was determined from single crystal x-ray shown in Figure 4-1 which revealed some interesting ramifications.



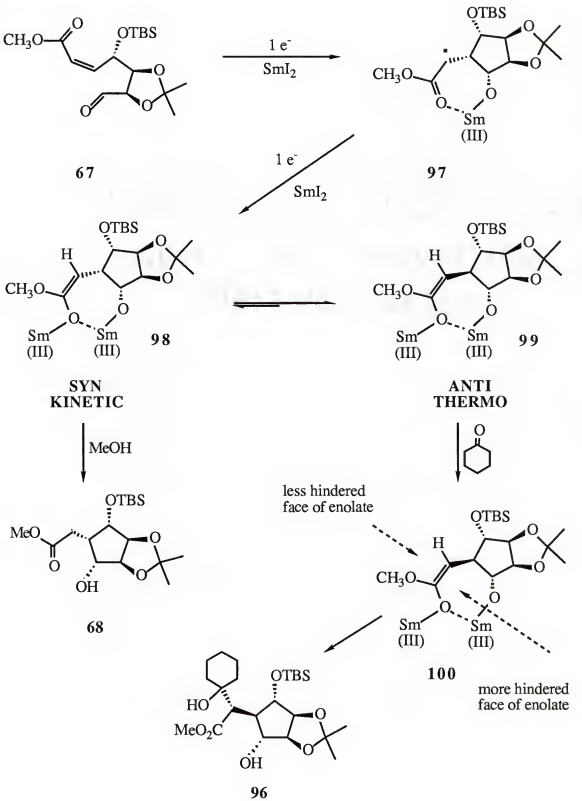
67 **96**

76%

structure from crystal x-ray

Scheme 4-4

It was intriguing to discover that the stereochemistry of the two newly formed ring appendages was diametric of what was expected. In a similar experiment employing the same carbohydrate derivative but using methanol as a quencher instead, the stereochemistry on the single product was reversed (Chapter 3). It was apparent that the cis olefin in the starting substrate did not yield a syn product when a carbonyl was used to quench

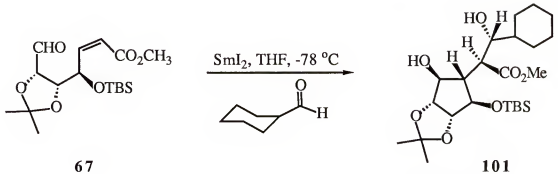

OTBS
CH3O
1 e-
SmI2
Sm
(III)
67
97
98
99
SYN
KINETIC
ANTI
THERMO
MeOH
MeO
OH
68
less hindered
face of enolate
100
more hindered
face of enolate
HO
MeO2C
96

Scheme 4-5

the reaction mixture after completion of the cyclization process. The proposed mechanism illustrated in Scheme 4-5 accounts for the two different results. It is possible that after SmI_2 donates an electron to the carbonyl of the carbohydrate it then undergoes addition to the unsaturation forming the alkyl radical 97 in which presumably, the Sm(III) species forms a bidentate chelate. A second electron transfer from another equivalent of SmI_2 forms the organosamarium enolate 98. In the studies shown in Scheme 3-5, the enolate 98 is assumed to be the less energetically favorable kinetic intermediate since the two appendages are on the same face experiencing steric interactions. In the presence of a compliant proton donor the enolate 98 quickly gets trapped leading to the sterically encumbered alcohol 68 that retains the syn geometry of the two moeties. However, in the absence of a proton donor the syn kinetic intermediate 98 has apparently enough time to equilibrate to the more stable thermodynamic enolate 99 where the two newly formed moeties are as far as possible from each other. The sterochemistry of the third center is explained by the use of models where it becomes apparent that the addition to the ketone occurs from the less hindered β-face of the enolate yielding elaborated carbocycle 96 as the single observable product.

It is also interesting to note that for these sequential transformations the organosamarium intermediate could not be trapped by quenching the reaction mixture with cyclohexanone after completion of the cyclization process. Attempts to do so generated very little of the desired addition product. Therefore, it was speculated that since the carbonyl substrate was best added simultaneously with the carbohydrate template to the SmI_2 solution, the choices of electrophiles might be be limited to ones considered to be stable to the reduction conditions. The study in Scheme 4-6, in which an

aldehyde would be employed as a potential electrophile, seemed condemned to administer reduction and pinacolic products.



67 **101**

major isomer
structure from x-ray

Scheme 4-6

Nevertheless, an attempt to record the results of such an effort seemed a worthwhile endeavor and the reaction shown in Scheme 4-6 was conducted. Suprisingly, when substrate 67 was subjected to the SmI_2-THF solution at -78 °C with an excess (2 eq.) of cyclohexane carboxaldehyde, two products were obtained in a 2:1 ratio in a total yield of 83% after chromatography. Compound 101 was the major isomer and its stereochemistry was determined from an x-ray crystallography shown in Figure 4-2. The x-ray confirmed the anti geometry of the first carbon-carbon bond to be identical to the stereochemistry of the previous product. It is speculated that the stereochemistry of the other minor isomer is similar to compound 101 and differs only at the alcohol center next to the cyclohexane ring. This is expected because of the use of a carbonyl compound with prechiral faces which can create a fourth chiral center. It is most intriguing that out of 16 possible isomers only 2 were observed.

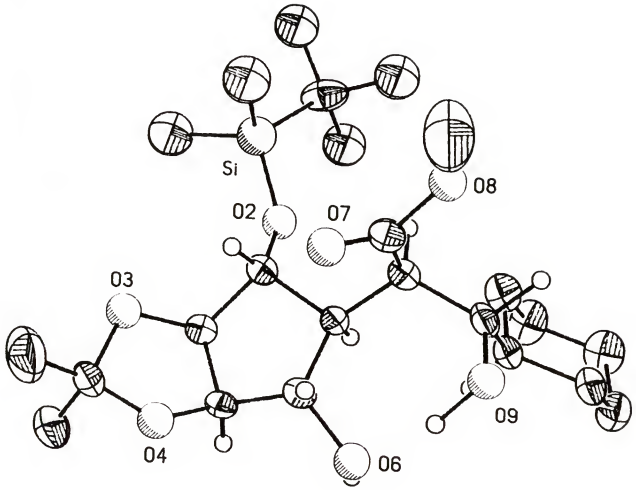
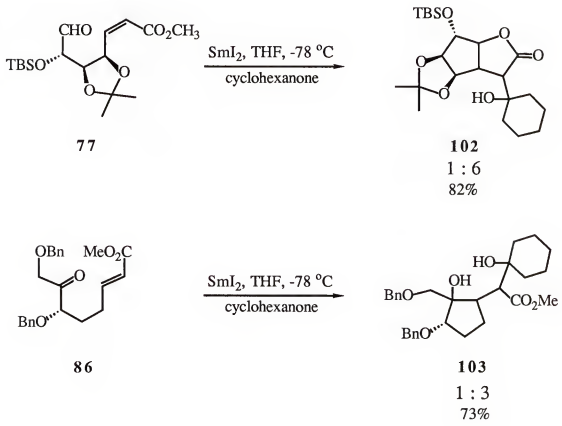


Figure 4-2

Crystal x-ray structure for carbocycle 101

Cyclohexanone as an electrophile was examined with two other different carbohydrate templates as seen in Scheme 4-7. Cis-lyxose derivati-



77

102
1 : 6
82%

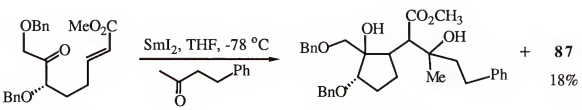
86

103
1 : 3
73%

Scheme 4-7

ve 77 reacted to give a mixture of two isomers in a ratio of 1:6 by ^1H NMR. The total yield was 82% after chromatography. The lactone 102 was the major product and the nonlactonized one being the minor isomer. Neither product has been obtained in crystalline form, thus their exact stereochemistry is still under investigation. However, the fact that one of them is a lactone indicates that the two ring appendages must be syn disposed to each other. Trans-glucal derivative 86, under the same reaction

conditions, rendered a 1:3 mixture of two isomers 103 in 73% yield after chromatography.

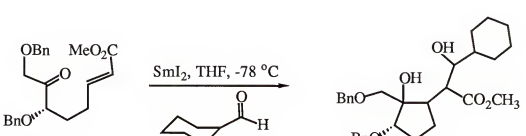


86

104
1 : 1
70%

Scheme 4-8

The reaction in Scheme 4-8 is interesting because it was the only one that rendered a small amount (18% yield) of the cyclic untrapped product 87 along with the addition products. This was also observed in Molander's studies as compound 95 in Scheme 4-3. This cyclized utrapped material is



86

105
1 : 3
73%

Scheme 4-9

generated because the electrophile used in this case was benzyl acetone, a methyl ketone. Apparently, the cyclized organosamarium intermediate is

basic enough to deprotonate the methyl ketone at rates competitive with nucleophilic addition. The other two products 104 were isolated in 70% yield as a 1:1 mixture of only two isomers.

The last example studied was the reaction of the glucal derivative 86 with SmI_2 with a cyclohexyl carboxaldehyde trap as seen in Scheme 4-9. Again, only two products were obtained out of 16 possible isomers which were isolated as a mixture of two isomers in a ratio of 1:3 and a 73% yield after chromatography. Note, that a single carbon center on the starting substrate is controlling the stereochemistry of all four new centers in the final product. The major product 105 was obtained as a crystalline solid and its stereochemistry is to be determined pending x-ray studies.

CHAPTER 5
EXPERIMENTAL SECTION

General

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer and are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz on a Varian VXR-300 (300 MHz) spectrometer and a General Electric QE 300. ^{13}C NMR spectra were recorded at 75 MHz on a Varian VXR-300 spectrometer and a General Electric QE 300 specrtometer. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (CH_4Si) as an internal standard in $CDCl_3$. Exact mass measurements were performed on an AEI M530 mass spectrometer. Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA 30091.

All reactions were run under an inert atmosphere of argon using flame-dried apparatus. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography and NMR spectroscopy. Temperatures below ambient temperature refer to bath temperatures unless otherwise stated. Solvents and anhydrous reagents were dried according to established procedures by distillation under nitrogen from an appropriate drying agent: ether and THF from benzophenone ketyl; dichloromethane from CaH_2. Other solvents were used "as received" from the manufacturer.

Analytical TLC was performed using E. Merck precoated silica gel plates (0.25 mm) using phosphomolybdic acid in ethanol as an indicator. Column chromatography was performed using E. Merck silica gel 60 (230-400 mesh) by standard flash and suction chromatographic techniques.

Experimental Procedures and Results

General experimental procedure for the preparation of enals 20, 21, 27, 30.

To a solution of 2-hydroxytetrahydropyran 24 (1.0 eq.) in $CHCl_3$ (1 M) a catalytic amount of benzoic acid (spatula tip) was added, to ensure nonbasic conditions, along with the stabilized ylid Ph_3P=CH-EWG (3.0 eq.). After 24-48 h, TLC analysis indicated that the lactol was consumed and the reaction mixture was quenched with H_2O. Extraction with ether (3X50 mL) followed by flash chromatography isolated the unsaturated alcohol products. Subsequently, the alcohols were stirred in CH_2Cl_2 (0.5 M) along with pyridinium dichromate (2.0 eq.), acidic acid (gla., a catalytic amount) and ground molecular sieves. The reaction mixture was stirred for 48-52 h and TLC analysis indicated that the starting material was consumed. The reaction mixture was then diluted to 4 volumes with ether and stirred for 1 h. It was filtered through celite and concentrated in vacuo. Flash chromatography over silica gel rendered the desired enals 20, 21, 27, 30.

Trans aldehyde 20

The compound was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.47 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.77 (m, 1H), 6.92 (m, 1 H), 5.83 (m, 1 H), 3.72 (s, 3 H), 2.49, (m, 2 H), 2.25 (m, 2 H), 1.81 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 201.27, 166.49, 147.67, 121.53, 51.12, 42.64, 30.99, 20.07; IR (neat oil) 2950, 2710, 1710, 1650, 1180, 730 cm^{-1}; mass spectrum (EI) 156 (1.6), 129 (21), 111 (34), 108 (24), 100 (100), 87 (35), 81 (33), 69 (31); exact mass calculated: $C_8H_{12}O_3$, 156.0786; found: 156.0792.

Cis Aldehyde 21

The compound was identified by direct comparison with spectra provided by Dr.xR.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.48 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.78 (m, 1H), 6.23 (m, 1 H), 5.83 (m, 1 H), 3.70 (s, 3 H), 2.70 (ABq, 2 H, J = 1.8 Hz), 2.49 (ABq, 2 H, J = 1.5 Hz), 1.79 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 202.03, 166.62, 148.90, 120.313, 51.07, 43.16, 28.09, 21.12; IR (neat oil) 2585, 2560, 1720, 1610, 1440, 1400, 1170, 1005, 810 cm^{-1}; mass spectrum (EI) 156 (0.8), 155 (7.3), 124 (37), 113 (68), 100 (68), 81 (100); exact mass calculated: $C_8H_{12}O_3$, 156.0786; found: 156.0785.

Trans aldehyde 27

The spectroscopic properties of 27 clearly indicated that it was the trans aldehyde identical to that reported by A. A. Baum.[20(b)] Rf 0.43 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1 H), 7.27 (m, 5 H), 6.38 (d, 1 H, J = 15.9 Hz), 6.15 (d of t, 1 H, J = 15.6, 6.9 Hz), 2.45 (ABq, 2 H, J = 7.5 Hz), 2.49 (ABq, 2 H, J = 7.5 Hz), 1.79 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 202.25, 137.35, 130.85, 129.29, 128.59,

128.42, 128.10, 126.98, 125.88, 43.05, 32.14, 21.55; IR (neat oil) 2940, 2825, 2720, 1940, 1870, 1725, 1600, 1490, 1450, 975 cm^{-1}; mass spectrum (EI) 174 (19), 131 (11), 130 (100), 117 (40), 115 (53), 104 (7.5), 91 (28); analysis, calculated C: 82.72%, H: 8.10%; found C: 82.79%, H: 8.12%.

Trans aldehyde 30

Physical data for aldehyde 30 are as follows: Rf 0.16 (30% ether-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 9.82 (s, 1 H), 6.48 (m, 1 H), 5.39 (m, 1 H), 2.53 (m, 4 H), 1.82 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 201.30, 154.70, 117.24, 100.44, 42.56, 32.24, 19.83; IR (neat oil) 2940, 2840, 2730, 2218, 1765, 1720, 1718, 1640, 1450, 1390, 1170, 1020, 740 cm^{-1}; mass spectrum (EI), no M^+ observed 149 (42), 123 (15), 95 (34), 83 (25), 79 (29), 67 (100) cm^{-1}.

General experimental procedure for the preparation of enones 33, 36, 37.

The morpholine enamine of cyclohexanone or cyclopentanone[31] (1.0 eq.) was stirred in ether (0.5 m). To the flask acrolein (1.1 eq.) was added at 0 °C and the reaction was stirred at room temperature for 15 h. HCl (2.0 M; 1.1 eq.) was then added to the contents of the flask at room temperature and the reaction was stirred for 0.5 h. The reaction mixture was subsequently diluted with EtOH and extracted with H_2O. Flash chromatography over silica gel afforded the ketone aldehyde. This material then was subjected to a standard Wittig reaction by dissolving it in CH_2Cl_2 (0.5 M) and with methyl(triphenylphosphoranylidene)acetate (2.0 eq.) The reaction was complete after 2 h as indicated by TLC analysis. The reaction mixture was

then concentrated and flash chromatography rendered the desired enones 33, 36, and 37.

Trans cyclohexanone 33

The compound was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.51 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.95 (m, 1 H), 5.83 (m, 1 H), 3.74 (s, 3 H), 2.28 (m, 5 H), 2.17 to 1.86 (m, 5 H), 1.65 (t, 1 H, J = 14.4 Hz), 1.34 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 212.52, 166.97, 149.00, 121.07, 51.33, 49.64, 42.08, 33.99, 29.63, 27.94, 27.70, 24.96; IR (neat oil) 2920, 2860, 1728, 1710, 1650, 1450, 1430, 1290, 1258, 1030 cm^{-1}.

Trans cyclopentanone 36

The compound was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.58 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.05 (m, 1 H), 5.86 (m, 1 H), 3.73 (s, 3 H), 2.36 to 1.38 (m, 11 H); IR (neat oil) 2960, 2865, 1728, 1740, 1660, 1410, 1438, 1275, 1175, 1040, 985 cm^{-1}.

Cis cyclopentanone 37

The compound was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.62 (50% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.22 (d of t, 1 H, J = 7.5, 11.4 Hz), 5.80 (d of t, 1 H, J = 1.5, 11.7 Hz), 3.72 (s, 3 H), 2.74 (m, 2 H), 2.28 (m, 2 H), 2.17 to 1.28 (m, 7 H); IR (neat oil) 2960, 2880, 1735, 1740, 1645, 1440, 1410, 1010, 1030, 1060, 1120, 1180, 1205, 920, 825 cm^{-1}.

General experimental procedure for the cyclization of simple carbocycles 22, 23, 28, 29, 31, 32, 34, 35, 38, 39.

Addition of a THF-methanol (3:1; v:v) solution of the starting substrate to a solution of SmI_2 (2 equivalents) and THF (~ 0.03 M in the starting material) was carried out dropwise at 0 °C over 5 minutes in an inert atmosphere. Starting substrates were consumed as indicated by TLC analysis within 5-10 minutes and subsequently the reactions were quenched with aqueous $NaHCO_3$. Simple work up with ether and separation by flash chromatography resulted in isolation of the desired cyclopentyl alcohols.

Anti cyclopentyl alcohol 22

Compound 22 was identified by direct comparison with spectra provided by Dr. R. D. Little.[17(f,g)] Its physical data are as follows: Rf 0.67 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 3.86 (ABq, 1 H, 3.9 Hz), 3.69 (s, 3 H), 2.92 (b s, 1 H), 2.44 (d of d, 2 H, J = 3.6, 10.2 Hz), 1.98 (m, 2 H), 1.75 (m, 3 H), 1.58 (m, 1 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 174.35, 78.38, 51.51, 44.12, 37.88, 33.88, 33.30, 21.52; IR (neat oil) 3400, 2950, 2870, 1740, 1435, 1195, 1170, 725 cm^{-1}.

Syn-[3.3.0]-lactone 23

Compound 23 was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.52 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 5.00 (t, 1 H, 7.2 Hz), 2.81 (m, 2 H), 2.29 (m, 1 H), 1.82 to 1.69 (m, 6 H); IR (neat oil) 2900, 2875, 1760, 1355, 1170, 1090, 1040, 980, 900 cm^{-1}.

Anti-xydroxybenzyl cyclopentyl alcohol 28

Compound 28 was also identified by direct comparison with spectra from the literature.[20(a)] Its physical data are as follows: Rf 0.46 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 3.88 (m, 1 H), 2.76 (d of d, 1 H, J = 6.9, 13.8 Hz), 2.52 (d of d, 1 H, J = 8.1, 13.2 Hz), 2.08 to 1.21 (m, 8 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 141.09, 128.81, 128.37, 125.91, 76.60, 49.80, 39.76, 34.12, 29.77, 21.44; IR (neat oil) 3360, 3080, 3060, 3020, 2950, 2870, 1600, 1495, 1450, 1070, 905, 730, 700 cm^{-1}; mass spectrum (EI) 176 (27), 158 (28), 130 (12), 129 (14), 117 (25), 92 (100), 85 (29); analysis, calculated C: 81.78%, H: 9.15%; found C: 81.71%, H: 9.16%.

Syn-hydroxybenzyl cyclopentyl alcohol 29

Compound 29 was also identified by direct comparison with spectra from the literature.[20(a)] Its physical data are as follows: Rf 0.24 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 4.09 (b s, 1 H), 2.85 (d of d, 1 H, J = 7.8, 13.5 Hz), 2.68 (d of d, 1 H, J = 7.5, 13.5 Hz), 2.08 to 1.27 (m, 8 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 141.87, 128.70, 128.34, 125.73, 74.41, 47.64, 35.50, 34.84, 28.75, 21.81; IR (neat oil) 3400, 3080, 3060, 3020, 2940, 2870, 1600, 1495, 1450, 1025, 980, 750, 690 cm^{-1}; mass spectrum (EI) 176 (5.4), 159 (38), 158 (88), 130 (42), 129 (44), 117 (68), 115 (21), 104 (11), 92 (44), 91 (100), 80 (28), 77 (13).

Anti-hydroxymethylenenitrile cyclopentyl alcohol 31

This compound was isolated as an inseperable 2.7:1 mixture of anti 31 : syn 32 isomers. Physical data reported for major isomer 31 are as follows: Rf 0.16 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.28 (m, 1 H), 2.56 (d of d, 1 H, J = 8.1, 16.8 Hz), 2.43 (d of d, 1 H, J = 7.2, 16.8), 2.13 (m, 1 H), 1.91 (m, 3 H), 1.73 to 1.45 (m, 4 H); 75 MHz ^{13}C

NMR ($CDCl_3$) δ 119.97, 73.63, 41.89, 35.12, 28.86, 21.92, 17.21; IR (neat oil) 3443, 2962, 2875, 2250, 1422, 1154, 1107, 1035, 909 cm^{-1}; mass spectrum (EI) 125 (8.1), 108 (7.0), 97 (20), 96 (66), 82 (27), 80 (14), 69 (54), 67 (41), 57 (65); exact mass calculated: $C_7H_{11}ON$, 125.0840; found: 125.0849.

Anti-bicyclo-[4.3.0]-alcohol 34

Compound 34 was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.38 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 3.67 (s, 3 H), 2.64 (b s, 1 H), 2.49 (m, 1 H), 2.52 (m, 2 H), 1.90 (m, 1 H), 1.70 to 1.15 (m, 11 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 174.81, 76.57, 51.66, 46.64, 44.62, 33.87, 28.10, 26.68, 23.85, 23.27, 20.95, 20.11; IR (neat oil) 3042, 2845, 2920, 1730, 1435, 1310, 1270, 1155, 1020, 995 cm^{-1}.

Anti-bicyclo-[4.3.0]-alcohol 34a (bridgehead isomer)

Compound 34a was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.37 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 3.68 (s, 3 H), 2.25 (d of d, 1 H, J = 4.2, 13.5 Hz), 1.91 (m, 1 H), 1.68 (m, 4 H), 1.52 (m, 4 H), 1.24 (m, 7 H); IR (neat oil) 3051, 2850, 2920, 1705, 1720, 1435, 1320, 1215, 1170, 1140, 960 cm^{-1}.

Syn-bicyclo-[4.3.0]-lactone 35

Compound 34a was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.37 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 2.84 (d of d, 1 H,

J = 11.2, 17.5 Hz), 2.63 (m, 1 H), 2.39 to 1.08 (b m, 14 H); IR (neat oil) 2920, 2845, 1765, 1450, 1195 cm^{-1}.

Anti-bicyclo-[3.3.0]-alcohol 38

Compound 38 was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.29 (25% ether-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H), 3.39 (b s, 1 H), 2.48 (m, 2 H), 2.24 (m, 2 H), 2.12 (m, 1 H), 1.88 (m, 1 H), 1.67 (m, 3 H), 1.29 (m, 3 H), 1.03 (m, 1 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 175.03, 90.88, 51.66, 51.23, 46.50, 36.80, 34.81, 34.43, 31.11, 29.47, 25.52; IR (neat oil) 3440, 2950, 2870, 1730, 1715, 1430, 1205, 1160, 1000, 905, 730 cm^{-1}.

Syn-bicyclo-[3.3.0]-lactone 39

Compound 39 was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Its physical data are as follows: Rf 0.38 (25% ether-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 2.76 (m, 1 H), 2.53 (m, 1 H), 2.38 (m, 2 H), 2.12 to 1.25 (b m, 10 H); IR (neat oil) 2925, 2860, 1780, 1760, 1460, 1450, 1290, 1220, 1165, 1030, 985, 955 cm^{-1}.

Pinacol 19

Physical data for compound 19 are as follows: Rf 0.41 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 5.82 (m, 2 H), 5.00 (m, 4 H), 3.87 (m, 1 H), 3.58 (m, 2 H), 3.43 (m, 1 H), 2.10 (m, 4 H), 1.65 to 1.25 (m, 8 H); IR (neat oil) 3350, 2920, 1640, 1065, 908 cm^{-1}; mass spectrum (EI), no M^+ observed, 181, 163, 100, 81, 67, 55.

Diacetate ketone (48)

Tri-O-acetyl-D-glucal (3.93 g, 0.0144 mol) was refluxed in water (50 mL) for 1 h until TLC plate indicated that the reaction was complete. The reaction mixture was extracted with EtOAc (3X80 mL) dried with $MgSO_4$ and placed in a 100 mL flask with EtOAc (28.9 mL; 0.5 M) with Pd on C (10%; 0.32 g) and fitted with an H_2 balloon. It was stirred overnight (16 h) and next day ^1H NMR indicated the absence of the alkene. Flash chromatography over silica gel gave 2.76 g (84%) of clear oil. This material was stirred in $CHCl_3$ (1M; 12.09 mL), with a catalytic amount of benzoic acid (spatula tip), to ensure nonbasic conditions, along with methyl(triphenylphosphoranylidene)acetate (6.06 g). After 18 h, TLC analysis indicated completion of the reaction and the contents of the flask were diluted with hexanes (1 vol) and concentrated under reduced pressure. Chromatography over silica gel gave the Wittig product as an inseparable mixture of geometric isomers (8:1) trans:cis by ^1H NMR integration. This mixture then was stirred in CH_2Cl_2 (0.5 M; 24.2 mL) along with pyridinium dichromate (9.0 g) and a small amount of crushed molecular sieves. A few drops of glacial acetic acid were also added. After 12 h the reaction was diluted to 4 volumes with ether and let to stir for 1 h. Subsequently, it was filtered through celite and concentrated under vacuo. Flash chromatography over silica gel using 100% ether gave 2.05 g of diacetate ketone 49.

Physical data are as follows: 300 MHz ^1H NMR ($CDCl_3$) δ 6.93 (m, 1H), 5.86 (d of d, 1 H, J = 1.5, 15.6 Hz), 5.14 (d of d, 1 H, J = 4.8, 7.8 Hz), 4.80 (ABq, 2 H, J = 17.5 Hz), 3.74 (s, 3 H), 2.34 (ABq, 2 H, J =

9.9 Hz), 2.17 (s, 6 H), 2.02 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 20.18, 20.32, 27.29, 28.73, 51.36, 66.87, 75.33, 121.98, 146.7, 166.51, 169.96, 170.11, 200.32; IR (neat oil) 2958, 2860, 2460, 2360, 1730, 1660, 1440, 1370, 1170, 1025 cm^{-1}; analysis, calculated C: 54.53%, H: 6.34%; found C: 54.59%, H: 6.37%.

Cyclopentyl alcohol 51

Compound 51 was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Physical data are as follows: 300 MHz ^1H NMR ($CDCl_3$) δ 3.68 (s, 3 H), 2.70 (s, 1 H), 2.45 (d of d, 1 H, J = 3.9, 7.9 Hz), 2.26 (m, 2 H), 1.96 (m, 1 H), 1.82 to 1.49 (m, 4 H), 1.25 (m, 1 H), 1.15 (s, 3 H); IR (neat oil) 3410, 2950, 1720, 1453, 1265, 1150 cm^{-1}; exact mass $C_9H_{14}O_2$, calculated: 154.0993; found: 154.1009.

Unsaturated methyl ketone 50

Ketone 50 was identified by direct comparison with spectra provided by Dr. R.D. Little.[17(f,g)] Physical data are as follows: 300 MHz ^1H NMR ($CDCl_3$) δ 6.93 (d of t, 1 H, J = 6.9, 15.6 Hz), 5.84 (d of t, 1 H, J = 1.5, 15.9 Hz), 3.73 (s, 3 H), 2.46 (t, 2 H, J = 7.2 Hz), 2.22 (m, 2 H), 2.14 (s, 3 H), 1.75 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 208.09, 166.93, 148.36, 121.58, 51.48, 42.52, 31.30, 29.98, 21.93; IR (neat oil) 2940, 1740, 1430, 1260, 1190, 1090, 1035, 975 cm^{-1}; exact mass $C_9H_{14}O_3$, calculated: 170.0929; found: 170.0946.

1-O-Benzyl-3,4-O-isopropylidine-(L)-arabinose (72)

D-(-)-arabinose (100g; 0.666 mol) was placed in a 500 mL flask with a funnel along with benzyl alcohol (undistilled, taken as solvent; 350 mL)

and pTsOH (cat. amount; 3.10 g) and stirred well with a stirring rod. It was then warmed to 95 °C (solution temperature; bath temperature 120 °C) and magnetic stirring was applied for 10-15 minutes until the solution became clear. The solution was cooled to 60 °C, poured with stirring into a beaker containing a solution (2,000 mL) of hexanes-ether (40:60; v:v) and subsequently cooled to 0 °C in an ice chest. After 60 minutes the solvents were poured out and the white paste, which had settled out, remained behind. The white paste was the crude wet sugar product 71 contaminated with some BnOH. Next, this paste was dissolved into a solution of acetonedimethoxypropane (500 mL : 150 mL) along with a catalytic amount of p-toluenesulfonic acid (3.0 g). The reaction mixture became clear after 20 minutes of stirring but TLC plate showed some unreacted starting material present. After 2 h, aqueous saturated $NaHCO_3$ (200 mL) and water (300 mL) were added. Extraction with ethyl acetate (3 X 500 mL), concentration of the organic layers under reduced pressure and suction chromatography gave 86.64 g (46.4%) of product 72. An analytical sample of the hydroscopic white crystals was obtained by recrystallization from ethyl acetate.

Physical data are as follows: mp: 55-56 °C; Rf 0.42 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H), 4.93 (d, 1 H, J = 3.6 Hz), 4.67 (center of AB q, 2 H, J = 11.7 Hz), 4.22 (m, 2 H), 3.97, (d of d, 1 H, J = 13.2, 2.4 Hz), 3.93 (d of d, 1 H, J = 13.2, 1.2 Hz), 3.80 (m, 1 H), 2.28 (d, 1 H, J = 1.6 Hz), 1.54, (s, 3 H), 1.37 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 136.67, 128.46, 128.14, 127.98, 109.42, 97.32, 76.43, 74.47, 69.62, 67.33, 62.86, 27.45, 25.60; IR (neat oil) 3410, 2980, 1488, 1448, 1370, 1235, 1205, 1088, 1043 cm^{-1}; mass spectrum (EI), no M^+ observed, 265 (1.5), 189 (3.4), 131 (20.2), 92 (28.1), 91

(100), 85 (27.9), 65 (11.1), 59 (66.4), 57 (22.6), 43 (27.6); analysis, calculated C: 59.99%, H: 6.71%; found C: 59.93%, H: 6.75%.

2-O-(t-butyldimethylsilyl)-3,4-O-isopropylidine-(L)-arabinose (66)

A 1000 mL round-bottom flask, under Ar, containing compound 72 (86.64 g; 0.309 moles), CH_2Cl_2 (309 mL), Et_3N (82.21 mL) and a catalytic amount of 4-DMAP (7.54 g) was cooled to 0 ^oC with an ice bath. At that temperature, TBSCl (60.29 g) was added to the reaction mixture. The ice bath was removed after one hour, and the reaction mixture stirred for 96 h. An additional amount of Et_3N (41.1 mL) and TBSCl (46.3 g) were added after 24 h. When the reaction had gone to completion as determined by TLC analysis, it was quenched by pouring into the reaction flask aqueous saturated $NaHCO_3$ (500 mL) and ice (~500 g). Extraction of the aqueous layer with a 90:10 solution of hexane:ether (2 X 500 mL), followed by concentration of the organic layers under reduced pressure, gave a crude tan oil (~200 ml). This crude material was then diluted with THF (160 mL) in a 3-neck flask, equipped with a large stirring bar and a dry ice condenser. About 250 mL of NH_3 were condensed in the flask and enough THF was added until the reaction mixture was one phase. Li wire was added (4-5" of 1/2" in diameter) until a blue color persisted for 8 minutes. The reaction was then cautiously quenched with a 50:50 mixture of $(BrCH_2)_2$:THF. After 20 minutes, solid NH_4Cl followed by aqueous saturated NH_4Cl were added in small amounts. It was then extracted with EtOAc (3 X 500 mL) and $CHCl_3$ (1 X 500 mL). The organic layers were then concentrated in vacuo, dried with $NaSO_4$, and suction chromatography (300 mL fractions; 100% hexane to 100% ether) gave a nearly pure slightly

yellow oil (50.4 g). After two subsequent chromatographies, 44.6 g of pure lactol (66) were obtained. Analytically pure crystals were obtained from pentanes (150 mL) at 0 °C .

Physical data are as follows: mp 82-83.5 °C; R_f 0.52 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.66 (d of d, 1 H, J = 7.8, 4.2 Hz), 4.24 (m, 1 H), 4.13 (apparent triplet, 1 H), 4.03 (d of d, 1 H, J = 13.2, 2.43 Hz), 3.87 (d of d, 1 H, J = 13.2, 3.03 Hz), 3.71 (apparent triplet, 1 H), 3.23 (d, 1 H, J = 7.8 Hz), 1.54 (s, 3 H), 1.36 (s, 3 H), 0.91 (s, 9 H), 0.13 (d, 6 H, J = 0.6 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 109.77, 96.38, 77.52, 72.75, 72.71, 62.43, 27.46, 25.72, 25.57, 18.06, -5.02, -4.63; IR (neat oil) 3444, 2925, 2882, 2842, 2480, 1445, 1240, 1118, 1025, 832, 754 cm^{-1}; mass spectrum (EI), no M^+ observed, 289 (2.5), 247 (3.6), 189 910.3), 171 (13.30), 143 (69.9), 133 (20.6), 131 (36.2), 101 (22.5), 75 (100), 73 (45.6), 59 (33.4), 43 (38.6); analysis calc. C: 55.23%, H: 9.27%; found C: 55.32%, H: 9.27%.

Cis-arabinose alcohol

A mixture of lactol 66 (204 mg; 0.671 mmol), methyl(triphenylphosphoranylidene)-acetate (2.20 g; 0.00658 mol) and benzoic acid (0.02 g; 0.00164 mol) in $CHCl_3$ (1.0 M; 0.67 mL) was stirred for 48 h at room temperature until lactol (66) was consumed as determined by TLC analysis. The reaction mixture was then directly subjected to flash chromatography over silica gel without any work-up. Total isolated material was 178.3 mg (74%), obtained as a 10:1 (Z:E) mixture of geometric isomers. Physical data are reported for the Z-isomer.

Physical data are as follows: R_f 0.41 (35% THF-hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 6.19 (d of d, 1 H, J = 12.0, 9.0 Hz), 5.67 (d of d, 1 H, J = 12.0, 2.0 Hz), 5.43 (m, 1 H), 4.19 (m, 1 H), 4.08 (m, 1 H), 3.70 (m, 1 H), 3.78 (m, 1 H), 3.62 (s, 3 H), 2.54 (s, br, 1 H), 1.39 (s, 3 H), 1.23 (s, 3 H), 0.80 (s, 9 H), -0.05 (s, 3 H), -0.10 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 166.14, 149.20, 119.70, 108.69, 80.07, 78.23, 67.28, 61.58, 51.38, 26.88, 25.74, 25.25, 18.01; IR (neat oil) 3460, 2942, 2902, 2860, 1718, 1645, 1190, 1040, 830, 770 cm^{-1}; mass spectrum (EI), no M^+ observed, 361 (0.18), 345 (2.3), 230 (27.5), 189 (9.3), 143 (25.1), 131 (73.2), 117 (21.7), 115 (29.9), 89 (28.4), 75 (83.1), 73 (72.7), 59 (100).

Cis-arabinose aldehyde (67)

A mixture of the above alcohol (167.8 mg; 0.4648 mmol), pyridinium dichromate (350 mg; 0.930 mmol), 2 drops of glacial acetic acid and crushed 3 Å molecular sieves (catalytic amount) in CH_2Cl_2 (0.93 mL; 0.5 M) were stirred for 24 h at room temperature. When the reaction was complete (to about 95%) as determined by TLC analysis, the mixture was diluted with ether (20 mL) and let to stir for about an hour. This dilute solution was then suction-filtered through celite followed by multiple washings by ethyl acetate. Concentration under reduced pressure followed by flash chromatography gave 121.5 mg (72.8%) of the title compound (67).

Physical data are as follows: ^{1}NMR ($CDCl_3$) δ 9.75 (m, 1 H), 6.23 (d of d, 1 H, J = 12.0, 8.0 Hz), 5.43 (d, 1 H, J = 8.0 Hz), 4.46 (d of d, 1 H, J = 8.0, 2.0 Hz), 4.42 (d of d, 1 H, J = 8.0, 1.0 Hz), 3.70 (s, 3 H), 1.55 (s, 3 H), 1.31 (s, 3 H), 0.83 (s, 9 H), 0.20 (s, 3 H), 0.00 (s, 3 H);

75 MHz ^{13}C NMR ($CDCl_3$) δ 200.47, 166.00, 150.03, 119.26, 110.72, 82.83, 80.88, 66.80, 51.51, 26.42, 25.79, 25.01, 0.04; IR (neat oil) 2960, 2930, 2858, 1730, 1710, 1648, 1438, 1215, 1190, 1070, 832, 775 cm^{-1}; mass spectrum (EI), no M^+ observed, 229 (23), 201 (14), 185 (13), 129 (30), 89 (55), exact mass calculatedd for M-15 (loss of methyl), $C_{16}H_{27}O_6Si$: 343.1577; found: 343.1588.

Cyclic alcohol (68)

The cis-aldehyde 67 (42 mg; 0.117 mmol) was drawn into a syringe with 1mL total solution of THF:MeOH (3:1; v:v) and added dropwise to a cooled (-78° C) solution of SmI_2 (0.1 M; 3.51 mL) over a period of 5 minutes. The reaction was complete after 5 minutes. The reaction mixture was then quenched with aqueous saturated $NaHCO_3$ and extracted with ether. The organic layers were concentrated and after flash chromatography 25.7 mg (69%) of product 68 were obtained.

Physical data are as follows: Rf 0.52 (35% THF-hexanes) 300 MHz ^1H NMR ($CDCl_3$) δ 4.58 (d of d, 1 H, J = 6.9, 1.5 Hz), 4.45 (d of d, 1 H, J = 6.5, 2.5 Hz), 3.92 (m, 2 H), 3.72 (s, 3 H), 3.43 (s, br, 1 H), 2.70 (d of d, 1 H, J = 16.5, 6.3 Hz), 2.48 (d of d, 1 H, J = 16.5, 8.4 Hz), 2.39 (m, 1 H), 1.48 (s, 3 H), 1.30 (s, 3 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 173.59, 111.50, 86.04, 85.69, 51.88, 50.00, 34.82, 26.15, 25.71, 24.08, 17.84, 0.03; IR (neat oil) 3430, 2921, 2855, 1733, 1075, 840, 775, 665, cm^{-1}; mass spectrum (EI), no M^+ observed, 303 (852), 227 (29.6), 153 (33.3), 129 (41.6), 89 (34.1), 75 (100), 73 (72.7), 59 (41.0); exact mass calculated for M-15 (loss of methyl), $C_{16}H_{29}O_6Si$: 345.1733; found: 345.1730.

Cyclic diol (69)

The cyclic alcohol 68 (25.1 mg; 0.0695 mmol) was stirred in THF (70 μL; 1 M). To this solution nBu_4NF (139 μL; 1 M in THF) was added dropwise via syringe over period of 2 minutes. Reaction had gone to completion after 15 minutes as indicated by TLC analysis. The reaction mixture was then quenched with aqueous saturated $NaHCO_3$, extracted with EtOAC (3 X 5 mL) and the combined EtOAc layers were concentrated under reduced pressure. Flash chromatography over silica gel gave 5.7 mg of symmetrical compound 69 as a clear oil.

Physical data are as follows: Rf 0.15 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 4.45 (s, 2 H), 3.90 (d, 2 H, J = 8.0 Hz), 3.73 (s, 3 H), 2.68 (d, 2 H, J = 7.0 Hz), 2.35 (m, 1 H), 1.49 (s, 3 H), 1.31 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 174.33, 112.36, 85.29, 79.75, 52.14, 49.20, 35.33, 26.52, 24.37; IR (neat oil) 3406, 2923, 1713, 1440, 1370, 1208, 1157, 1057, 856.

Lyxose lactol (73)

To a stirred suspension of an anomeric mixture of 1-0-Benzyl-L-Lyxose (5.02 g; 0.0334 mol) and 30 mL of acetone, 10 mL of dimethoxypropane and 0.5 g of p-toluenesulfonic acid were added. After 12 h at room temperature, 70 mL of hexane-diethyl ether (1:1 mixture) was added, and the solution was washed once with aqueous sodium bicarbonate solution and twice with water. It was then concentrated in vacuo. The resulting material was chromatographed over silica gel to yield 5.86 g of a colorless oil as a mixture of anomers. Rf 0.38, 0.37 (35% THF-hexanes).

An analytical sample of the higher Rf anomer was isolated by chromatography and its physical data is as follows: Rf 0.22 (25% THF-hexane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.82 (d, 1 H, J = 2.4 Hz), 4.64 (center of AB q, 1 H, J = 12.0 Hz), 4.23 (m, 2 H), 3.79 (m, 3 H), 3.27 (d, 1 H, J = 7.2 Hz), 1.48 (s, 3 H), 1.33 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$), δ 136.69, 128.49, 128.16, 128.01, 109.45, 97.33, 76.37, 74.47, 69.67, 67.34, 62.94, 27.44, 25.59; IR (neat oil) 4309, 2967, 2924, 2866, 1458, 1450, 1370, 1213, 905 cm^{-1}; mass spectrum (EI), no M^+ observed, 189 (14.3), 131 (77.9), 91 (100), 85 (23.8), 59 (62.8), 57 (25.7); analysis, calculated C: 64.27%, H: 7.19%; found C: 64.15%, H:7.40%.

The above compound (5.71 g; 0.0204 mol) was placed in a 100 mL flask with CH_2Cl_2 (20.4 mL; 1 M), Et_3N (11.35 mL) and a catalytic amount of 4-DMAP (0.468 g). Lastly, TBSCl (6.12 g) was added and the reaction was stirred under Ar athmosphere for 48h. When reaction was gone to completion it was quenched with aqueous saturated $NaHCO_3$ and exctracted with ether (3 X 100 mL). The organic layers were then concentrated under reduced pressure and the crude product was used without further purification in the next reaction. It was then placed in a 3-necked flask and dissolved in 20 mL THF. Approximately 20 mL NH_3 were condensed at -78 ^oC into this solution and small pieces of lithium metal were added until the solution color remained blue for 8 minutes. It was then carefully quenched with 1,2-dibromoethane-THF (1:1, v:v) solution, followed by a small amount of solid ammonium chloride and a small amount of aqueous saturated ammonium chloride. Ammonia was evaporated by passing N_2 gas through the solution. Extraction with ethyl acetate, concentration of the organic layers in vacuo and flash chromatography gave 4.96 g (80% over two steps) as a homogeneous 1:1 mixture of anomers 73.

Upon standing crystals formed and a single isomer was obtained (1.14 g) as white powder after recrystalization from cold pentanes.

Physical data are as follows: Rf 0.42 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 5.14 (d of d, 1 H, J = 7.6, 2.1 Hz), 4.22 (m, 2 H), 4.10 (m, 1 H), 3.82 (m, 3 H), 1.50 (s, 3 H), 1.07 (s, 3 H), 0.82 (s, 9 H), 0.25 (s, 3 H), 0.21 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 109.26, 92.29, 75.75, 75.46, 68.51, 62.81, 27.30, 25.68, 25.39, 17.99, -0.01; IR (KBr pellet) 3400, 2926, 1240, 1125, 1052, 840 cm^{-1}; mass spectrum (EI), no M^+ observed, 289 (3.1), 171 (11.22), 143 (100), 101 (41.9), 75 (85.3), 69 (39.9), 59 (52.3), 43 (57.1); analysis, calculated C: 55.23%, H: 9.27%; found C: 55.29%, H: 9.27%.

Cis- and trans-lyxose alcohols (76) and (74)

Lyxose Lactol 73 (460 mg; 1.51 mmol) was stirred in $CHCl_3$ (1.51 mL; 1.0 M) under Ar atmosphere. To that, methyl(triphenylphosphoranylidene)acetate (1.015 g) was added along with a catalytic amount of benzoic acid (36 mg). Reaction mixture stirred for 52 h. When TLC analysis indicated that the reaction was complete, it was quenched with brine and extracted first with ether (2 X 15 mL) and then with ethyl acetate (2 X 15 mL). The organic layers were then concentrated in vacuo and chromatography over silica gel gave 435.6 mg (80%) of a mixture of (~ 2:1) Z:E isomers. The two isomers cis-76 and trans-74 were isolated upon chromatography.

Physical data for the E isomer 75: Rf 0.47% (50% ether-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.91 (d of d, 1 H, J = 15.6, 6.9 Hz), 6.52 (d, 1 H, J = 15.6 Hz), 4.64 (apparent t, 1 H, J = 6.9 Hz), 4.33 (d of d, 1

H, J = 7.2, 6.9 Hz), 3.79 (m, 1 H), 3.77 (s, 3 H), 3.63 (m, 1 H), 3.50 (m, 1 H), 1.52 (s, 3 H), 1.37 (s, 3 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.14 (s, 3 H); 75Hz ^{13}C NMR ($CDCl_3$), δ 166.25, 143.40, 123.49, 109.25, 79.24, 76.20, 71.70, 63.77, 51.75, 27.72, 25.85, 25.23, 18.24; IR (neat oil) 3480, 2940, 2920, 2850, 1710, 1650, 1248, 830 cm^{-1}; mass spectrum (EI), no M^+ observed, 361 (1.1), 129 (30.01), 117 (100), 98 (49.4), 97 (40.2), 75 (56.8), 73 (68.5), 59 (39.2); analysis, calculated C: 56.65%, H:8.89%; found C: 56.68%, H: 9.01%.

Physical data for Z isomer 76: Rf 0.49 (50% ether-hexanes); 300 MHz ^1H NMR ($CDCl_3$), δ 6.39 (d of d, 1 H, J = 11.4, 7.0 Hz), 5.93 (d of d, 1 H, J = 11.4, 1.5 Hz), 5.67 (m, 1 H), 4.48 (d of d, 1 H, J = 6.6, 5.7 Hz), 3.75 (s, 3 H), 3.65 (m, 3 H), 2.35 (m, 1 H), 1.54 (s, 3 H), 1.39 (s, 3 H), 0.92 (s, 9 H), 0.11 (s, 3 H), 0.12 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.06, 145.82, 120.87, 109.03, 80.04, 73.37, 71.27, 64.32, 51.59, 27.52, 25.97, 25.35, 28.29, -4.19, -4.25; IR (neat oil) 3460,2920, 2850, 1718, 1435, 1370, 1298, 1192, 1055, 830 cm^{-1}; mass spectrum (EI), no M^+ observed, 245 (16.2), 227 (41.7), 185 (50.7), 153 (32.7), 127 (41.9), 121 (26.4), 117 (100), 111 (31.4), 99 (41.4), 98 (49.2), 97 (32.2), 89 (57.3), 83 (23.8), 75 (75.8), 73 (88.4), 59 (53.4), 57 (20.21); analysis, calculated C: 56.65%, H: 8.89%; found C: 56.92%, H: 9.04%

Trans-lyxose aldehyde (75)

Oxidation of the trans alcohol 75 (22.0 mg; 0.0609 mmol) was accomplished by stirring it in CH_2Cl_2 (0.305 mL) along with pyridinium dichromate (68.8 mg) a catalytic amount of crushed molecular sieves and a catalytic amount of glacial acetic acid (1 drop). Reaction was completed

after 8h. It was diluted with ether and stirred for half an hour. Suction filtration over a small bed of silica gel gave 10.1 mg (60%) of pure aldehyde 76.

Physical data are as follows: Rf 0.69 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.99 (d of d, 1 H, J = 15.6, 5.4 Hz), 6.11 (d of d, 1 H, J = 15.6, 1.5 Hz), 4.87 to 4.93 (m, 1 H), 4.40 (apparent t, 1 H, J = 6.3 Hz), 4.06 (d, 1 H, J = 5.7 Hz), 3.55 (s, 3 H), 1.47 (s, 3 H), 1.61 (s, 3 H), 0.95 (s, 9 H), 0.12 (s, 3 H), 0.13 (s, 3 H); 75 Hz ^{13}C NMR ($CDCl_3$), δ 201.40, 142.71, 122.95, 79.02, 76.19, 51.65, 26.78, 25.72, 25.66, 24.92, -4.64, -5.04; IR (neat oil) 2953, 2931, 2897, 2361, 2857, 1797, 1662, 1558, 1472, 1463, 1437, 1381, 1306, 1195, 1006, 810, 669 cm^{-1}; mass spectrum (EI), no M^+ observed, 343 (3.6), 243 (25), 215 (27), 187 (55), 185 (83), 127 (47), 117 (42), 99 (33), 98 (27), 89 (32), 83 (25), 75 (65), 73 (100); exact mass for M-15 (loss of methyl) $C_{16}H_{27}O_6Si$, calculated: 343.1576, found: 343.1560.

Cis-lyxose aldehyde (77)

In the same manner as above 76 was oxidized by stirring it (225.2 mg; 0.623 mmol) with CH_2Cl_2 (2.50 mL; 0.25 M), pyridinium dichromate (0.703 g), a catalytic amount of 3Å crushed molecular sieves and 1 drop of glacial acetic acid. The reaction was complete after 10 h. It was diluted with ether (10 mL) and quick flash chromatography over silica gel gave 180 mg (81%) of 77 as a clear thick oil.

Physical data are as follows: Rf 0.68 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$), δ 9.68 (s, 1 H), 6.5 (d of d, 1 H, J = 11.9, 7.0 Hz), 5.91 (d, 1 H, J = 11.9 Hz), 5.66 (apparent t, 1 H, J = 7.0 Hz), 4.82 (d of

d, 1 H, J = 3.5, 0.9 Hz), 3.91 (m, 1 H), 3.76 (s, 3 H), 1.56 (s, 3 H), 1.39 (s, 3 H), 0.95 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 202.97, 165.97, 147.14, 120.52, 109.59, 79.47, 77.65, 75.08, 51.60, 26.41, 25.74, 24.96, 18.09, 0.03; IR (neat oil) 2922, 2853, 1795, 1720, 1115, 830 cm^{-1}; mass spectrum (EI), no M^+ observed, 343 (0.64), 243 (11), 187 (14), 185 (16), 183 (11), 127 (100), 117 (15), 101 (12), 99 (54), 89 (20), 75 (54), 73 (93); exact mass for M-15 (loss of methyl), $C_{16}H_{27}O_6Si$, calculated: 343.1577, found: 343.1558.

Syn-cyclic alcohol (78)

The cis-aldehyde 77 above (42.0 mg; 0.117 mmol) was drawn into a syringe with a solution of 1 mL THF:MeOH (3:1; v:v) and added dropwise to a cooled solution (-78 °C) of SmI_2 (3.6 mL; 0.1 M in THF) over a period of 5 minutes. The solution was kept at -78 °C for 1 h. When the reaction was complete as indicated by TLC analysis, it was quenched with aqueous saturated $NaHCO_3$ solution (1 mL). Chromatography using 50:50 solution of ether:hexane gave 31.0 mg (73%) of the pure syn-cyclic alcohol 78.

Physical data are as follows: Rf 0.41 (35% THF-hexanes); 300 MHZ ^1H NMR ($CDCl_3$) δ 4.45 (d of d, 1 H, J = 7.5, 4.5 Hz), 4.39 (d of d, 1 H, J = 7.5, 3.0 Hz), 4.21 (d of d, 1 H, J = 8.0, 4.5 Hz), 4.09 (d of d, 1 H, J = 5.0, 3.0 Hz), 3.68 (s, 3 H), 2.74 (m, 1 H), 2.52 (m ,1 H), 2.46 (m, 1 H), 1.46 (s, 3 H), 1.26 (s, 3 H), 0.90 (s, 9 H), 0.14 (s, 3 H), 0.16 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 173.15, 112.17, 85.38, 83.09, 79.30, 75.13, 51.68, 44.57, 32.04, 27.05, 25.74, 24.63, 17.98, 0.02; IR (neat oil) 3520, 2925, 1735, 1251, 1209, 1055, 835, 778; mass spectrum

(EI), no M^+ observed, 213 (15), 185 (100), 157 (12), 129 (17), 75 (61), 73 (41), 55 (44); analysis, calculated C: 56.63%, H: 8.95%; found C: 58.62%, H: 8.91%.

Lyxose lactone (80)

The syn-cyclic alcohol 78 (91 mg; 0.252 mmol) was stirred in THF (0.250 mL; 1 M). To the flask nBu_4NF (0.750 mL; 1 M in THF) was added in one shot. Immediately the reaction mixture turned dark. After 10 minutes TLC experiment indicated that the starting material was consumed. The reaction was then diluted with 6 volumes of ether and quenched with (1 mL) aqueous saturated $NaHCO_3$. Extraction with ether, followed by flash chromatography over silica gel gave 25.3 mg (47%) of lactone 80.

Physical data are as follows: mp: 104-106 °C; Rf 0.27 (35% THF-hexane) 300 MHz ^1H NMR ($CDCl_3$) δ 5.12 (d of d, 1 H, J = 8.1, 4.2 Hz), 4.62 (apparent m, 2 H), 3.39 (d, 1 H, J = 4.2 Hz), 2.93 to 3.02 (m, 1 H), 2.73 (d of d, 1 H, J = 17.7, 11.1 Hz), 2.45 (d of d, 1 H, J = 17.7, 9.0 Hz), 2.29 (broad s, 1 H), 1.44 (s, 3 H), 1.28 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 177.80, 124.51, 124.51, 106.15, 74.86, 67.88, 45.58, 33.02, 27.26, 24.94; analysis, calculated C: 56.07%, H: 6.59%; found C: 56.12%, H: 6.63%; structure absolutely configured by single crystal x-ray.

Anti-cyclic alcohol (79)

The trans-aldehyde 75 (10.0 mg; 0.0279 mmol) was drawn into a syringe with a solution of 0.60 mL THF:MeOH (3:1; v:v) and added dropwise to a cooled solution (-78 °C) of SmI_2 (0.83 mL; 0.1 M in THF) over a period of 5 minutes. After 20 minutes it was quenched with aqueous sat-

urated $NaHCO_3$ solution (1 mL) and extracted with ether. ^1H NMR on the crude product indicated a 1:4 mixture of two isomes. Flash chromatography over silica gel afforded 6.4 mg of the pure major product 79 (64%).

Physical data are as follows: Rf 0.42 (35% THF-hexane) 300 MHz ^1H NMR ($CDCl_3$) δ 4.69 (t, 1 H, J = 5.4 Hz), 4.30 (d, 1 H, J = 6.9 Hz), 3.96 (d, 1 H, J = 4.5 Hz), 3.54 (m, 3 H), 3.53 (s, 1 H), 2.67 (d, 1 H, J = 2.4 Hz), 2.64 (s, 1 H), 1.46 (s, 3 H), 1.25 (s, 3 H), 0.56 (s, 9 H), 0.32 (s, 3 H), 0.28 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 173.79, 110.19, 82.85, 77.70, 75.86, 74.82, 51.65, 42.02, 31.10, 25.96, 25.78, 25.73, 25.68, 18.09, -4.95, -4.55; IR (neat oil) 3552, 2952, 2930, 2857, 2360, 2341, 1472, 1463, 1437, 1373, 1259, 1209, 1163, 11256, 1005, 985, 940, 778, 687 cm^{-1}; mass spectrum (EI), no M^+ observed, 345 (5.26), 227 (32.0), 213 (50.5), 185 (96.9), 153 (57.3), 129 (67.4), 75 (98.3), 73 (66.7); exact mass for M-15 (loss of methyl $C_{16}H_{29}O_6Si$, calculated: 345.1773, found: 345.1744.

Di-acetonide ester (81)

Anti-alcohol (79) from above (4.3 mg; 0.01877 mmol) was stirred with a 3:1 (v:v) mixture of 2,2-dimethoxypropane and acetone (1 mL total) along with a catalytic amount (a spatula tip) of pTSOH for 40 minutes. Chromatography was performed on a pipette using a solution of 30% hexane-ether and 4.8 mg (95%) of pure product 81 were isolated .

Physical data are as follows: Rf 0.54 (35% THF-hexane) 300 MHz ^1H NMR ($CDCl_3$) δ 4.77 (apperant t, 1 H, J = 4.9 Hz), 4.57 (d, 1 H, J = 5.32 Hz), 4.38 (m, 2 H), 2.67 (d of d, 1 H, J = 9.8, 16.4 Hz), 2.58 (d of d, 1 H, J = 5.4, 16.4 Hz), 2.45 (m, 1 H), 1.96 (s, 3 H), 1.82 (s, 3 H),

1.59 (s, 3 H), 1.55 (s, 3 H); IR (neat oil) 2922, 2850, 1732, 1439, 1374, 1258, 1209, 1162, 1057, 870, 797 cm^{-1}; mass spectrum (EI), no M^+ observed, 271(18), 231 (34), 199 (16), 153 (23), 139 (37), 111 (23), 97 (56), 85 (22), 73 (22), 59 (67), 43 (100); exact mass for M-15 (loss of methyl), $C_{13}H_{19}O_6$, calculated: 271.1182, found: 271.1186.

D-glucal lactol (85)

Tri-O-acetyl-D-glucal (3.0 g; 0.01102 mol) was stirred in benzene (11.02 mL; 1.0 M) in a flame-dried flask, along with trimethylsilylethanol (2.37 mL) and a catalytic amount of $BF_3.OEt_2$ (0.271 ml). The reaction was complete after 24h as indicated by TLC analysis. It was quenched with aqueous saturated $NaHCO_3$ and worked up with EtOAc (3 X 100 mL). Concentration of the organic layers in vacuo gave 3.27 g (90%) of crude product 82 which was subjected in catalytic hydrogenation. Crude material was stirred in EtOAc (22 mL; 0.5 M) along with a catalytic amount (a couple of spatula tips) of Pd on C . The reaction was under H_2 for 6.4 h. When the hydrogenation was complete as ^1H NMR indicated, the reaction mixture was passed through celite and concentrated under reduced pressure. Subsequently, this crude diacetate alcohol (assume 11.02 mmol) was stirred in MeOH (22.8 mL; 0.5 M) along with a large excess (6.31 g) of K_2CO_3 until done by TLC. After 14 h, the reaction was quenched with H_2O extracted with EtOAc and concentrated under reduced pressure. Meantime, NaH (60% in oil suspension) was dried with pentanes (5 mL, two treatments) and then diluted with dry THF (20.50 mL). The crude material 83 (assumed 11.02 mmol) was then added at 23 ^oC dropwise in the THF-NaH mixture. After 10 minutes benzyl bromide (3.39 mL) was added

and the reaction was refluxed for 4 hours. The reaction progress was monitored by TLC. When gone to completion it was quenched with H_2O and extracted with ether (3 X 100 mL). Crude material 84 was concentrated under vacuo and stirred in CH_2Cl_2 (25 mL) at 23 °C. To the flask, CF_3CO_2H (50 mL) was added and immediately the reaction darkened markedly. After 10 minutes, isopropyl acetate (20 mL) was added and the reaction was quenched slowly with 12 M NaOH. Extraction and concentration of the organic layer in vacuo, followed by flash chromatography over silica gel using a solution of 50:50 (v:v) ether-hexane afforded 1.70 g (47% from a 5 step process) of tan oil 85. An anlytical sample was crystalized fron a cold solution of ether - hexane and the white crystals were used for characterization.

Physical data are reported as a *ca.* 1:1 mixture of anomers: mp: 63-65 °C; Rf 0.48 (35% THF-hexane) 300 MHz ^1H NMR ($CDCl_3$) δ 7.25 (m, 10 H), 5.28 (d, J = 3.2 Hz, anomer A), 4.79 (d, J = 6.0 Hz, anomer B), 4.55 (m, 3 H), 4.41 (d, J = 4.0 Hz, anomer A), 4.37 (d, J = 4.0 Hz, anomer B), 4.06 (m, 1 H), 3.68 (m, 2 H), 3.42 (m, 1 H), 2.89 (b s, 1 H), 1.45 to 2.60 (m, 4 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 138.34, 138.05, 128.22, 127.55, 127.48, 95.79, 90.74, 77.80, 73.34, 73.30, 73.23, 72.59, 71.04, 71.00, 70.49, 69.60, 31.12, 28.94, 27.25, 23.16; IR (KBr pellet) 3400, 3060, 3030, 2930, 2860, 2420, 1590, 1495, 1450, 1358, 1315, 1217, 1056, 985, 900, 730, 690 cm^{-1}; mass spectrum (EI), no M^+ observed, 311 (2.70, 181 (15), 131 (13), 107 (13), 92 (32), 91(100), 69 (10), 65 (32); analysis calculated C: 73.14%, H: 7.36%; found C: 72.75%, H: 7.37%.

Trans-glucal ketone (86)

Lactol 86 from above (210 mg; 0.639 mmol) was stirred in $CHCl_3$ (640 μL; 1.0 M) at 23 °C. To the flask, a catalytic amount (20 mg) of benzoic acid was added in order to maintain acidity along with methyl(triphenylphosphoranylidene)-acetate (429 mg). After 3 h the reaction had gone to completion. It was directly placed on a chromatography column (no workup) and flash chromatography using 100% ether gave 183.7 mg (75%) of pure trans-alcohol.

Physical data are as follows: Rf 0.63 (35% THF-hexane; double elusion); 300 MHz ^1H NMR ($CDCl_3$) δ 7.29 (m, 10 H), 6.88 (d of t, 1 H, J = 6.9, 15.6 Hz), 5.74 (d of t, 1 H, J = 1.5, 15.6 Hz), 4.53 (m, 4H), 3.88 (m, 1H), 3.70 (s, 3 H), 3.64 to 3.48 (m, 4 H), 2.18 to 2.46 (m, 3 H), 1.73 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.99, 149.16, 138.13, 137.78, 128.46, 128.41, 127.85, 127.77, 121.08, 78.57, 73.48, 72.34, 71.44, 70.95, 51.36, 28.45, 27.76; IR (neat oil) 3450, 3025, 2940, 2900, 2860, 2400, 1715, 1490, 1450, 1430, 1265, 1200, 1160, 1070, 730, 695 cm^{-1}; mass spectrum (EI) 385 (1.6), 181 (24), 111 (12), 92 (40), 91 (100), 79 (16); analysis, calculated C: 71.85%, H: 7.34%; found C: 71.91%, H: 7.37%.

This alcohol then (183 mg; 0.476 mmol) was stirred in CH_2Cl_2 (0.95 μL; 0.5 M) at 23 °C. To the flask, pyridinium dichromate was added (358 mg) along with a small amount of 3Å molecular sieves (finely ground), and 20 μL of glacial acetic acid. After 12 h, TLC indicated the reaction was complete. The reaction mixture was then diluted 4 volumes with ether and was let to stir for 0.5 h. Subsequentely, it was filtered through celite and concentrated in vacuo. Flash chromatography over silica gel using 100% ether gave 150.3 mg (82%) of pure product 86.

Physical data are as follows: Rf 0.49 (35% THF-hexane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.27 (m,10 H), 6.89 (d of t, 1 H, J = 6.9, 15.6 Hz), 5.80 (d of t, 1 H, J = 1.5, 15.6 Hz), 4.57 (s, 2 H), 4.47 (AB q, 2 H, J = 11.7 Hz), 3.31 (AB q, 2 H, J = 18.0 Hz), 3.99 (t, 1 H, J = 6.3 Hz), 3.49 (s, 3 H), 2.28 (m, 2 H), 1.83 (m, 2 H); 75 MHz ^{13} C NMR ($CDCl_3$) δ 208.37, 166.59, 147.52, 136.88, 136.85, 128.41, 128.41, 128.04, 127.92, 121.67, 81.89, 73.25, 72.61, 72.52, 51.28, 30.00, 27.51; IR (neat oil) 3030, 2940, 2920, 2850, 2375, 2240, 1710, 1640, 1430, 1265, 1090, 900, 690 cm^{-1}; mass spectrum (EI), no M^+observed, 111 (14), 107 (22), 105 (67), 92 (35), 91 (100), 77(48); analysis, calculated C: 72.23%, H: 6.85; found C: 72.16%, H: 6.89%.

Glucal cyclic alcohol (87)

The ketone 87 from above (211 mg; 0.549 mmol) was drawn into a syringe with a solution of MeOH-THF (3 mL total). In a flame dried flask, SmI_2 (16.48 mL; 0.1 M in THF) was cooled to 0 °C, and the contents of the syringe were added to the blue SmI_2 solution over a period of 4 minutes. After 0.5 h, the blue color turned yellow indicating the end of the reaction. The reaction was quenched with 1 mL aqueous saturated $NaHCO_3$ and diluted with ether (50 mL). After 15 minutes of stirring the solution was filtered and concentrated under vacuo. Flash chromatography over silica gel gave 177.2 mg (84%) of pure product 87.

Physical data are as follows: Rf 0.49 (35% THF-hexane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 10 H), 4.53 (m, 4 H), 3.35 (m, 1 H), 3.63 9s, anomer A), 3.58 (s, anomer B), 4.38 (AB q, 2 H, J = 12.0 Hz), 3.09 (s, 1 H0, 2.63 (d of d, 1 H, J = 6.0, 18.0 Hz), 2.44 (m, 1 H), 2.16 (d of

d, 1 H, J = 13.0, 18.0 Hz), 1.96 (m, 2 H), 1.74 (m, 1 H), 1.2 (m, 1 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 173.61, 138.14, 138.03, 128.37, 128.34, 128.25, 127.71, 127.68, 127.60, 127.36, 127.34, 85.78, 82.23, 80.81, 80.24, 73.78, 73.57, 71.65, 71.46, 69.88, 51.52, 44.04, 42.81, 35.99, 34.33, 27.70, 27.27, 27.18, 26.70; IR (neat oil) 3500, 3050, 3025, 2940, 2850, 2450, 2390, 1725, 1490, 1440, 1250, 1190, 1080, 1010, 900 cm^{-1}; analysis calculated C: 71.85%, H: 7.34%; found C: 71.93%, H: 7.39%.

Glucal lactone (90)

The cyclic alcohol 88 was subjected to catalytic hydrogenation for the removal of the benzyl protecting groups. It was stirred (226 mg; 0.588 mmol) in MeOH with a catalytic amount of HCl (10 μL) along with a spatula tip of Pd on carbon. After 60 h TLC indicated formation of the triol 89 which was isolated by chromatograpy in a 96% yield (115 mg). Subsequently, triol 88 was diluted with a 10:1 (v:v) solution of ϕ-THF in the presence of a catalytic amount of pTsOH. After 0.5 h, TLC indicated the complete formation of the lactone 89. It was diluted with 1 mL of EtOAc and passed through some celite on a pipete column. The isolated product was 48 mg (86%), pure by ^1H NMR. This lactone (5.2 mg; 0.0268 mmol) was then stirred with a mixture of acetone (0.75 mL) and 2,2diethoxypropane (0.25 mL), along with a catalytic amount (a spatula tip) of pTsOH. The reaction had gone to completion after 1.5 h by TLC analysis. Flash chromatography on a pipete column using silica gel and 100% ether gave 2.4 mg (39%) of protected lactone 90 in highly crystalline colorless needles.

Physical data are as follows: mp 133-134.5 °C; Rf 0.70 (80% benzene-EtOH); 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.45 (AB q, 2 H, J = 4.5 Hz), 4.19 (d, 1 H, J = 12.0 Hz), 2.47 (m, 1 H), 2.35 (m, 1 H), 2.25 (d of d, 1 H, J = 8.4, 15.0 Hz), 2.03 (m, 1 H), 1.77 (m, 2 H), 1.53 (m, 1 H), 1.48 (s, 3 H), 1.35 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 172.34, 111.50, 89.06, 85.02, 71.97, 42.72, 33.66, 30.58, 29.72, 27.30, 25.87; IR (KBr pellet) 2960, 2900, 2460, 2350, 1750, 1375, 1275, 1120, 1050 cm^{-1}; mass spectrum 213 (4.9), 197 (80), 137 (52), 95 (10), 93 (67), 81 (21), 67(220); analysis, calculated C: 62.27%, H: 7.60%; found C: 61.70%; H: 7.58%; structure absolutely configured by single crystal x-ray.

Arabinose diol (96)

Arabinose aldehyde 67 (60 mg; 0.195 mmol) was mixed with 1 mL THF and cyclohexanone (40.5 μL) and drawn into a syringe. SmI_2 solution in THF (0.1 M) was cooled to -78 °C and contents of the syringe were added dropwise over a period of 5 minutes. Seven minutes upon addition, TLC plate indicated that the reaction had gone to completion. It was quenched with $NaHCO_3$ and extracted with ether (3X25 mL). ^{1}H NMR of the crude product indicated the formation of a single isomer. Chromatography over silica gel gave 72.0 mg (81% yield) of crystaline product 96.

Physical data are as follows: mp 92-93.5 °C; Rf 0.54 (35% THF-hexane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.92 (b s, 1 H), 4.45 (d of d, 1 H, J = 3.9, 8.1 Hz), 4.28 (d of d, 1 H, J = 5.1, 7.8 Hz), 3.93 (m, 2 H), 3.74 (s, 3 H), 3.60 (d of d, 1 H, J = 5.1, 11.1 Hz), 2.94 (d, 1 H, J = 3.0 Hz), 2.37 (d of t, 1 H, J = 2.5, 10.8 Hz), 1.87 to 1.27 (b m, 9 H), 1.42 (s, 3 H), 1.27 (s, 3 H), 0.91 (s, 9 H), 0.14 (s, 3 H), 0.91 (s, 3 H); 75 MHz

^{13}C NMR ($CDCl_3$) δ −4.27, 0.00, 17.88, 21.34, 22.35, 25.37, 25.48, 25.79, 27.36, 34.27, 38.32, 50.35, 50.74, 51.44, 72.65, 73.99, 78.47, 84.27, 84.38, 112.59, 174.88; IR (KBr pellet) 3275, 2933, 2857, 1868, 1772, 1733, 1540, 1379, 1160, 1099, 864 cm^{-1}; mass spectrum 383 (26), 303 (25), 171 (47), 129 (43), 99 (24), 73 (100); analysis, calculated C: 60.23%, H: 9.23%; found C: 60.08%; H: 9.38%; structure absolutely configured by single crystal x-ray.

Arabinose diol (101)

Arabinose substrate 67 (138 mg; 384 mmol) was mixed with THF (1 mL) and cyclohexylcarboxaldehyde and drawn into a syringe. The contents of the syringe were added dropwise into a SmI_2 solution (0.1 M in THF; 10mL) at -78 °C. The reaction was complete after 4 minutes by TLC analysis. It was quenched by a small amount of $NaHCO_3$ and extracted with ether (3X25 mL). ^1H NMR of the crude product indicated the presence of two isomers in a ratio of 2:1. Flash chromatography separated the two products in a total yield of 83% (151.3 mg).

The major product 101 was obtained as white needles and its physical data are as follows: mp 141-143 °C; Rf 0.49 (35% THF-hexane); 300 MHz ^1H NMR ($CDCl_3$) δ 4.68 (s, 1 H), 4.45 (d of d, 1 H, J = 3.3, 7.9 Hz), 4.32 (d of d, 1 H, J = 5.2, 8.0 Hz), 4.02, (d of d, 1 H, J = 5.2, 10.9 Hz), 3.95 (d, 1 H, J = 3.7 Hz), 3.87 (d of d, 1 H, 3.3, 10.1 Hz), 2.99 (t, 1 H, 2.4 Hz), 2.18 (m, 2 H), 1.79 to 0.74 (m, 11 H), 1.45 (s, 3 H), 1.28 (s, 3 H), 0.89 (s, 9 H), 0.14 (s, 3 H), 0.07 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ −4.38, −3.02, 17.81, 25.52, 25.60, 25.66, 25.70, 26.25, 27.36, 27.80, 29.92, 39.30, 44.33, 50.20, 51.69, 74.09, 75.72, 78.54,

84.54, 112.48, 174.97; IR (KBr pellet) 3316, 2989, 2937, 1739, 1452, 1433, 1384, 1257, 1205, 1174, 1098, 1061, 1032, 869, 838 cm^{-1}; mass spectrum 397 (3.3), 187 (10.5), 129 (29), 103 (31), 89 (19), 77 (25), 73 (100); analysis, calculated C: 60.98%, H: 9.38%; found C: 60.48%; H: 9.49%; structure absolutely configured by single crystal x-ray.

The stereochemistry of the minor 101 product is still undetermined but its physical data are as follows: Rf 0.38 (35% THF-hexane); 300 MHz ^1H NMR ($CDCl_3$) δ 4.49 (δ, 1 H, 7.5 Hz), 4.34 (d of d, 1 H, J = 1.8, 6.6 Hz), 4.00 (d, 1 H, J = 4.5 Hz), 3.83 (d of d, 1 H, J = 2.1, 4.8 Hz), 3.64 (s, 3 H), 3.40 (d of d, 1 H, J = 2.7, 8.7 Hz), 2.83 (d of d, 1 H, J = 3.0, 9.6 Hz), 2.47 (m, 1 H), 1.96 (d, 1 H, J = 11.7 Hz), 1.64 to 0.81 (b m, 12 H), 1.37 (s, 3 H), 1.18 (s, 3 H), 0.78 (s, 9 H), 0.046 (s, 3 H), 0.008 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 25.55, 25.64, 25.71, 25.74, 26.30, 27.41, 27.85, 29.96, 39.33, 44.40, 50.31, 51.72, 74.18, 75.77, 78.63, 84.59, 112.51, 175.92; IR (neat oil) 3455, 2928, 2856, 1729, 1451, 1381, 1255, 1209, 1160, 1065, 859, 838, 778 cm^{-1}; mass spectrum 473 (5.6), 397 (10), 339 (10), 303 (21), 227 (11), 187 (15), 95 (28), 83 (29), 73 (100).

Glucal diol (103)

Glucal ketone 86 (0.457 g; 0.00137 mol) was mixed with cyclohexanone (269 μL) and THF (1.5 mL) and drawn into a syringe. The contents of the syringe were added dropwise over a period of 5 minutes into SmI_2 reagent (0.2 M in THF; 7 mL) at -78 °C. The reaction was complete after 20 minutes as indicated by TLC analysis. It was quenched with $NaHCO_3$ and extracted with ether (3X25 mL). ^1H NMR of the crude reaction mixture

indicated the presence of two isomers in a ratio of 1:3. The two isomers 103 were separated by flash chromatography in a total yield 73% (0.479 g).

Physical data of the major isomer 103 are as follows: mp 94-95 °C, Rf: 0.25 (50% ether-hexane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.27 9m, 10 H), 4.67 (ABq, 1 H, J = 12.0 Hz), 4.50 (s, 1H), 3.94 to 3.65 (b m, 4 H), 3.51 (s, 3 H), 3.16 (s, 1 H), 2.61 (m, 2 H), 2.10 to 1.13 (b m, 16 H);75 MHz ^{13}C NMR ($CDCl_3$) δ 21.63, 21.78, 22.01, 25.57, 25.78, 25.89, 26.40, 30.70, 35.20, 36.5543.73, 51.35, 54.96, 69.60, 71.94, 72.97, 73.33, 80.55, 85.73, 127.23, 127.27, 127.41, 127.62, 127.71, 127.79, 128.21, 128.31, 128.35, 128.37, 138.55, 139.10, 176.09; IR (KBr pellet) 3475, 3063, 2933, 2862, 1710, 1496, 1453, 1354, 1199, 1168, 1116 cm^{-1}.

Physical data of the minor isomer 103 are as follows: Rf: 0.20 (50% ether-hexane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 10 H), 4.55 (ABq, 2 H, J = 11.7 Hz), 4.55 (ABq, 2 H, J = 12.0 Hz), 3.92 (d of d, 1 H, J = 2.4, 6.0), 3.75 (d, 1 H, J = 10.2 Hz), 3.66 (s, 3 H), 3.38 (d of d, 1 H, J = 1.5, 10.5 Hz), 2.86 (d, 1 H, J = 1.5 Hz), 2.53 (m, 1 H), 2.37 (d, 1 H, J = 11.7 Hz), 2.26 (s, 1 H), 2.08 to 1.15 (b m, 14 H); MHz ^{13}C NMR ($CDCl_3$) δ 21.65, 21.84, 25.51, 26.65, 27.04, 35.62, 35.73, 46.01, 51.38, 54.76, 69.86, 69.93, 71.33, 72.71, 73.51, 77.55, 79.90, 82.00, 127.49, 127.55, 127.62, 127.79, 128.28, 128.37, 138.17, 138.36, 175.23; IR (neat oil) 3519, 3029, 2932, 2859, 1951, 1731, 1496, 1453, 1199, 1136, 1039, 1027, 979, 736 cm^{-1}.

Glucal diol (104)

Glucal ketone 86 (0.338 g; 0.00102 mol) was mixed with benzyl acetone (305 μL) and THF (1.0 mL) and drawn into a syringe. The contents of the syringe were added over a period of 5 minutes into a SmI_2 solution (0.2 M in THF; 5.0 mL) at -78 °C. Reaction was gone to completion after 10 minutes as indicated by TLC analysis. The products of the reaction were easily separated by flash chromatography. Products 104 were isolated in 70% yield as a 1:1 mixture of two isomers.

Physical data for isomer 104-a are: Rf 0.52 (35% THF-hexane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 15 H), 4.67 (ABq, 2 H, J = 14.3 Hz), 4.54 (s, 2 H), 3.88 (t, 1 H, J = 9.4 Hz), 3.75 (ABq, 2 H, J = 17 Hz), 3.56 (s, 3 H), 3.45 (s, 1 H), 2.78 (d, 1 H, J = 8.2 Hz), 2.75 to 2.54 (b m, 3 H), 2.07 to 1.70 (b m, 5 H), 1.33 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 25.43, 26.21, 29.80, 42.24, 44.61, 51.44, 54.21, 69.17, 71.97, 73.60, 74.08, 80.94, 85.60, 125.82, 125.84, 127.31, 127.46, 127.80, 138.82, 138.99, 142.01, 175.62; mass spectrum SELF-CI: m+1 533 (1.5), 315 (5.3), 300 (9.6), 181 (5.1), 91 (100).

Physical data for isomer 104-b are: Rf 0.43 (35% THF-hexane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 15 H), 4.66 (ABq, 2 H, J = 11.8 Hz), 4.75 (s, 2 H), 3.89 (t, 1 H, J = 8.7 Hz), 3.74 (ABq, 2 H, J = 10.2 Hz), 3.56 (s, 3 H), 3.53 (s, 1 H), 2.90 (s, 1 H), 2.77 (d, 1 H, J = 8.7 Hz), 2.66 (m, 2 H), 2.55 (ABq, 2 H, J = 10.2 Hz), 2.06 (m, 1 H), 1.82 (m, 4 H) 1.34 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 24.43, 25.60, 26.22, 30.35, 43.85, 44.53, 51.46, 54.38, 69.27, 71.95, 73.53, 74.06, 80.84, 85.59, 125.84, 127.27, 127.41, 128.26, 128.42, 137.27, 138.87, 142.04, 175.79; IR (neat oil) 3477, 3027, 2947, 2869, 1950, 1713, 1604, 1496, 1454, 1359, 1204, 1161, 1114, 732, 698 cm^{-1}.

Glucal diol (105)

Glucal ketone 86 (0.146 g; 0.00044 mol) was mixed with cyclohexyl carboxaldehyde (106 μL) and THF (1.0 mL) and drawn into a syringe. The contents of the syringe were added dropwise over a period of 5 minutes into SmI_2 reagent (0.2 M in THF; 3 mL) at -78 °C. The reaction was complete after 5 minutes. It was quenched with $NaHCO_3$ and extracted with ether (3X25 mL). ^1H NMR of the crude reaction mixture indicated the presence of two isomers in a ratio of 1:3. Flash chromatography separated the two isomers in a total yield of 73%.

Physical data for the minor 105 isomer: Rf 0.46 (35% THF-hexane); 300 MHz ^1H NMR ($CDCl_3$) δ 7.29 (m, 10 H), 4.63 (ABq, 2 H, J = 12 Hz), 4.55 (s, 2 H), 3.89 (t, 1 H, J = 8.2 Hz), 3.72 (ABq, 2 H, J = 9.3 Hz), 3.59 (s, 3 H), 3.20 (d of d, 1 H, J = 1.8, 9.3 Hz), 3.94 (b s, 1 H), 2.84 (d of d, 1 H, J = 2.1, 9.0 Hz), 2.59 (m, 2 H), 2.04 to 0.75 (b m, 14 H) ; 75 MHz ^{13}C NMR ($CDCl_3$) δ 23.90, 25.80, 25.89, 25.95, 26.34, 29.36, 29.95, 42.69, 45.15, 47.00, 51.53, 68.95, 71.92, 73.87, 75.31, 81.14, 85.98, 127.38, 127.48, 127.58, 127.74, 128.28, 138.15, 138.88, 176.11; IR (neat oil) 3473, 3063, 3029, 2926, 2852, 1712, 1452, 1352, 1274, 1201, 1163, 1027, 736, 698 cm^{-1}.

CHAPTER 5
SUMMARY

The studies described in this dissertation employed samarium diiodide as a reducing agent for the formation of carbon-carbon bonds in the preparation of highly functionalized carbocycles. The synthetic chemist can benefit from this research because highly oxygenated carbocyclic products process considerable synthetic utility due to their application in the total synthesis of biologically important molecules.

At the first stage, SmI_2 was used for the intramolecular reductive cyclization of ketones and aldehydes tethered to electron deficient olefins for the formation of simple five-membered carbocycles. The reaction employed SmI_2 (0.1 M; 3 eq.) in THF at 0 °C under dilute conditions (0.05 M) with methanol as a proton donor. Several electron- withdrawing groups were investigated. A small amount of pinacol dimer byproduct was observed in reactions where aldehydes were used. Ketones gave no 1,2-diol byproduct. With aldehyde starting materals, the (E)-geometric isomer gave a ratio only slightly favoring the anti-disposed product. In contrast, when cyclic ketones were used, a strong dependence of the product diastereoselectivity on the olefin geometry was observed. In one case, the (E)-geometric isomer produced the anti product (>250:1) nearly exclusively, while the (Z)-geometric isomer led to an almost equal anti:syn mixture of products.

This chemistry was next adapted to more complex unsaturated systems such as carbohydrates, which proved to be an excellent method for the

stereoselective preparation of polyhydroxylated carbocycles. These experiments demonstrated a strong correlation in the diastereoselectivity of the products depending on whether the olefin geometry of the starting carbohydrate was E or Z.

In a general scheme, protected carbohydrate underwent a Wittig reaction followed by an oxidation to produce the carbohydrate templates ready for the key reaction. When these substrates were treated with SmI_2, a reductive cyclization between the carbonyl and the β-carbon of the olefin rendered the desired polyhydroxylated cyclopentanes. In the overall sequence the sp^3 alcohol stereocenter at C-5 is destroyed when oxidation occurs and it is subsequently reinstated, upon treatment with SmI_2, to form a new hydroxyl bearing stereocenter. The most interesting observation in these studies is the correlation of the olefin geometry in the starting substrate with the product stereochemistry. It appears that the (Z)-olefin in the starting carbohydrate template favors the syn product and the (E)-olefin geometry favors the anti substrate.

In the last variation of this process, the proton donor in the key reaction was substituted for carbonyl electrophiles such as aldehydes and ketones. Thus, the ability of SmI_2 to promote sequential radical cyclization followed by carbonyl addition was also investigated. All sugar templates (upon treatment with SmI_2) underwent an initial radical olefin cyclization. Subsequently, reduction of the intermediate radical generated through this process produced a transient organosamarium enolate that was trapped *in situ* by aldehydes and ketones to produce carbocycles with two new carbon-carbon bonds.

In conclusion, these studies represent the first applications of the SmI_2 reagent to carbohydrates. After these seminal investigations, reac-

tions of carbohydrates with SmI_2 are currently under investigation by other research groups.[19(d)]

LIST OF REFERENCES

1. Trifonorov D.N. "The Price of Truth," Mir Publishers, Moscow, **1984**.

2. Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573.

3. Kagan, H. B. "Fundamental and Technological aspects of Organo-f-Elements Chemistry," Marks, T. J. and Fragala, I. L.; eds., NATO ASI, Dordrect, **1985**, pp 49-76.

4. Natale, N. R. *Organic Prep. and Procedures Int.* **1983**, *15,* 387.

5. Kagan, H. B.; Namy, J. L. *Divalent Lanthanides in Organic Chemistry* , in " Handbook on the Physics and Chemistry of Rare Earths," Gschneider, K. A. Jr.; Eyring, L.; eds., North Holland Publishing Co, Amsterdam, **1984**, 550.

6. For reviews on samarium diodide-mediated reactions see: a) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure and Appl. Chem.* **1988**, *60*, 1725; (b) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15; (c) Imamoto, T. *Reviews on Heteroatom Chemistry* **1990**, *3*, 87; (d) Inanaga, J. *Reviews on Heteroatom Chemistry* **1990**, *3*, 75; (e) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, Suppl. 1, *37*, 175.

7. Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chem.* **1977**, *1*, 5.

8. Kagan, H. B. *New J. Chem.* **1990**, *14*, 453.

9. (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Letters* **1986**, *27*, 3891; (b) Fukuzawa, S.; Nakanishi, A.; Fujinami T.; Sakai S. *J. Chem. Soc. Chem. Commun.* **1986**, 624; (c) Molander, G. A.; Kenny, C. *Tetrahedron Letters* **1987**, *28*, 4367; (d) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064; (e) Holton, R. A.; Williams, A. D. *J. Org. Chem.* **1988**, *53*, 5981; (f) Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Letters* **1989**, *30*, 2837; (g) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171.

10. (a) Daluge, S.; Vince, R. J. *Org. Chem.* **1978**, *43*, 2311, and references therein; (b) Wilcox, C. R.; Guadino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102; (c) RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522; (d) Suhadolnik, R. J. "Nucleotide Antibiotics," Wiley, New York, N.Y., 1970.

11. (a) Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 547; (b) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102.

12. (a) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *110*, 609; (b) RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522.

13. (a) Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116; (b) Giese, B. "Radicals in Organic synthesis: Formation of Carbon-Carbon Bonds," Pergamon Press, New York, **1986**; (c) Beckwith, A. L. J.; Ingold, K. U. *Free Radical Rearrangements,* in "Rearrangements in the Ground and Excited States," P. DeMayo, Ed. Academic Press, New York, **1980**; (d) Neumann, W. P. *Synthesis* **1987**, 665; (e) Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2268.

14. Molander, G. A. and Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778.

15. Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *111*, 8236.

16. (a) Fukuzawa, S.; Nakanishi, A., Fujinami, T.; Sakai, S. *J. Chem. Soc. Chem. Commun.* **1986**, 624; (b) Fukuzawa, S. I.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc. Chem Commun.* **1987**, 920; (c) Fukuzawa, S.; Nakanishi, A., Fujinami, T.; Sakai, S. *J. Chem. Soc. Perkin I* **1988**, 1669.

17. Enholm, E. J. and Trivellas A. *Tetrahedron Lett.* **1989**, 1063.

18. (a) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1987**, *100*, 545; (b) Miller, E.; Mahachi, T. *J. Org. Chem.* **1986**, *51*, 1041; (c) Pradhan, S. K.; Kadam, S. R.; Kolhe, J. N.; Radhakrishnan, S. V.; Sohani, V. B.; Thaker, J. *J. Org. Chem. 1981*, *46*, 2622; (d) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, 2821; (e) Ikeda, T.; Nishiguchi, I.; Omizu, H. *Chem. Lett.* **1976**, 1233; (f) Fox, D. P.; Little, R. D.; Baizer, M. M. *J. Org. Chem.* **1988**, *53*, 2287; (g) Little, R. D.; Fox, D. P.; Hijfte, L. V.; Dannecker, R.; Sowell, G.; Wollin, R. L.; Moens, L.; Baizer, M. Pertella, C. *Tetrahedron Lett.* **1985**, 4591.

19. (a) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2132; (b) Molander, G. A.; Kenny, C. *J. Am Chem. Soc.* **1989**, *111*, 8236; (c) Kahn, B. E.; Reike, R. D. *Chem. Rev.* **1988**, *88*, 733; (d) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125.

20. For comparison see references 17(f,g), and (a) Sehgal, R. K.; Koenigsberger, R. U.; renate, U.; Howard, T. J. *J. Chem. Soc. Perkin Trans. 1* **1976**, *2*, 191; (b) A. A. Baum, *Tetrahedron Lett.* **1972**, 1817.

21. Hoffmann, R., W. *Chem. Rev.* **1989**, *89*, 1841.

22. Molander, G. A.; Hahn, G. J. *J. Org. Chem.* **1986**, *51*, 1135.

23. Professor Padwa, A.; Emory University, Ga; (private communication).

24. For a review on the use of carbohydrate templates in synthesis, see: Hanessian, S. "Total Synthesis of Natural Products: the 'Chiron' Approach," Pergmon Press, Oxford, England, 1983.

25. Bartlett, P. A.; McLaren, K., L.; Ting, P., C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.

26. RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.

27. (a) Enholm, E. J. and Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463; (b) Enholm, E. J.; Satici, H. and Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841.

28. For a conseptually similar proof of syn stereochemistry in bicyclo[3.3.0]ring systems, see; Kigoshi, H.; Inamure, Y.; Niwa, H.; Yamada, K. *J. Am. Chem. Soc.* **1989**, *111*, 2302.

29. (a) Curran, D., P.; Fevig, T., L.; Totleben, M., J . *Synlett.* **1990**, 773; (b) Molander, G., A.; Harring, L., S. *J. Org. Chem.* **1990**, *55*, 6171.

30. Molander, G., A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439.

31. "Reagents for Organic Synthesis," Fieser, L. F.; Fieser, M., eds, J. Wiley and Sons, N.Y. N.Y., **1967**, pp 705-708.

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Antigone Trivellas was born in Athens, Greece in 1960. She finished high school in Thessaloniki in 1978. She came to the USA in 1979 where she did various things except study like she was supposed to. In 1984 she started school at Santa Fe Community College where she changed a lot of majors. Finally, she took up chemistry and transferred to University of Florida where she got her bachelor's degree in chemistry in 1988 and completed her Ph.D. in organic chemistry in 1991. She does not know what she is going to do with her life yet. Meantime, she continues her path in chemistry as a post-doc at Brown University.

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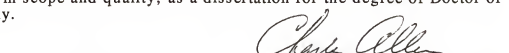

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